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(54) Title: SELECTIVE FACTOR Xa INHIBITORS

(57) Abstract

Novel compounds, their salts and compositions related thereto having activity against mammalian factor Xa are disclosed. The compounds are useful *in vitro* or *in vivo* for preventing or treating coagulation disorders.

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Selective Factor Xa Inhibitors

Field of the Invention

This invention relates to novel heterocyclic compounds which are potent and highly selective inhibitors of factor Xa or factor Xa when assembled in the prothrombinase complex. These compounds show selectivity for factor Xa versus other proteases of the coagulation (e.g. thrombin, fVIIa, fIXa) or the fibrinolytic cascades (e.g. plasminogen activators, plasmin).

Background of the Invention

Blood coagulation protects mammalian species when the integrity of the blood vessel wall is damaged and uncontrolled loss of blood threatens survival. Coagulation, resulting in the clotting of blood is an important component of hemostasis. Under normal hemostatic circumstances, there is maintained an acute balance of clot formation and clot removal (fibrinolysis). The blood coagulation cascade involves the conversion of a variety of inactive enzymes (zymogens) into active enzymes which ultimately convert the soluble plasma protein fibrinogen into an insoluble matrix of highly cross-linked fibrin. See Davie, *et al.*, "The Coagulation Cascade: Initiation, Maintenance and Regulation" Biochemistry 30:10363-10370 (1991). Blood platelets which adhere to damaged blood vessels are activated and incorporated into the clot and thus play a major role in the initial formation and stabilization of hemostatic "plugs". In certain diseases of the cardiovascular system, deviations from normal hemostasis push the balance of clot formation and clot dissolution towards life-threatening thrombus formation when thrombi occlude blood flow in coronary vessels (myocardial infarctions) or limb and pulmonary veins (venous thrombosis). Although platelets and blood coagulation are both involved in thrombus formation, certain components of the coagulation cascade are primarily responsible for the amplification or acceleration of the processes involved in platelet aggregation and fibrin deposition.

A key enzyme in the coagulation cascade as well as in hemostasis, is thrombin. Thrombin is intimately involved in the process of thrombus formation, but under normal

circumstances can also play an anticoagulant role in hemostasis through its ability to convert protein C into activated protein C in a thrombomodulin-dependent manner. Thrombin plays a central role in thrombosis through its ability to catalyze the penultimate conversion of fibrinogen into fibrin and through its potent platelet activation activity. Direct or indirect inhibition of thrombin activity has been the focus of a variety of recent anticoagulant strategies as reviewed by Claeson "Synthetic Peptides and Peptidomimetics as Substrates and Inhibitors of Thrombin and Other Proteases in the Blood Coagulation System", Blood Coag. Fibrinol. 5:411-436 (1994). The major classes of anticoagulants currently used in the clinic directly or indirectly affect thrombin (i.e. heparins, low-molecular weight heparins and coumarins). Thrombin is generated at the convergence of the intrinsic and extrinsic coagulation pathways by the prothrombinase complex. The prothrombinase complex is formed when activated Factor X (factor Xa) and its non-enzymatic cofactor, factor Va assemble on phospholipid surfaces in a Ca^{+2}-dependent fashion as reviewed by Mann, *et al.*, "Surface-Dependent Reactions of the Vitamin K-Dependent Enzymes", Blood 76:1-16 (1990). The prothrombinase complex converts the zymogen prothrombin into the active procoagulant thrombin.

The location of the prothrombinase complex at the convergence of the intrinsic and extrinsic coagulation pathways, and the significant amplification of thrombin generation (393,000-fold over uncomplexed factor Xa) mediated by the complex at a limited number of targeted catalytic units present at vascular lesion sites, suggests that inhibition of thrombin generation is an ideal method to block uncontrolled procoagulant activity. Unlike thrombin, which acts on a variety of protein substrates as well as at a specific receptor, factor Xa appears to have a single physiologic substrate, namely prothrombin.

Plasma contains an endogenous inhibitor of both the factor VIIa-tissue factor (TF) complex and factor Xa called tissue factor pathway inhibitor (TFPI). TFPI is a Kunitz-type protease inhibitor with three tandem Kunitz domains. TFPI inhibits the TF/fVIIa complex in a two-step mechanism which includes the initial interaction of the second Kunitz domain of TFPI with the active site of factor Xa, thereby inhibiting the

proteolytic activity of factor Xa. The second step involves the inhibition of the TF/fVIIa complex by formation of a quaternary complex TF/fVIIa/TFPI/fXa as described by Girard, *et al.*, "Functional Significance of the Kunitz-type Inhibitory Domains of Lipoprotein-associated Coagulation Inhibitor", Nature 338:518-520 (1989).

Polypeptides derived from hematophagous organisms have been reported which are highly potent and specific inhibitors of factor Xa. U. S. Patent No. 4,588,587 awarded to Gasic, describes anticoagulant activity in the saliva of the Mexican leech, *Haementeria officinalis*. A principal component of this saliva is shown to be the polypeptide factor Xa inhibitor, antistasin, by Nutt, *et al.*, "The Amino Acid Sequence of Antistasin, a Potent Inhibitor of Factor Xa Reveals a Repeated Internal Structure", J. Biol. Chem. 263:10162-10167 (1988).

Another potent and highly specific inhibitor of Factor Xa, tick anticoagulant peptide, has been isolated from the whole body extract of the soft tick *Ornithidoros moubata*, as reported by Waxman, *et al.*, "Tick Anticoagulant Peptide (TAP) is a Novel Inhibitor of Blood Coagulation Factor Xa", Science 248:593-596 (1990).

Other polypeptide type inhibitors of factor Xa have been reported including the following citations by: Condra, *et al.*, "Isolation and Structural Characterization of a Potent Inhibitor of Coagulation Factor Xa from the Leech *Haementeria ghilianii*", Thromb. Haemost. 61:437-441 (1989); Blankenship, *et al.*, "Amino Acid Sequence of Ghilanten: Anti-coagulant-antimetastatic Principle of the South American Leech, *Haementeria ghilianii*", Biochem. Biophys. Res. Commun. 166:1384-1389 (1990); Brankamp, *et al.*, "Ghilantens: Anticoagulants, Antimetastatic Proteins from the South American Leech *Haementeria ghilianii*", J. Lab. Clin. Med. 115:89-97 (1990); Jacobs, *et al.*, "Isolation and Characterization of a Coagulation Factor Xa Inhibitor from Black Fly Salivary Glands", Thromb. Haemost. 64:235-238 (1990); Rigbi, *et al.*, "Bovine Factor Xa Inhibiting Factor and Pharmaceutical Compositions Containing the Same", European Patent Application, 352,903 (1990); Cox, "Coagulation Factor X Inhibitor From the Hundred-pace Snake *Deinagkistrodon acutus* venom", Toxicon 31:1445-1457 (1993);

Cappello, *et al.*, "*Ancylostoma* Factor Xa Inhibitor: Partial Purification and its Identification as a Major Hookworm-derived Anticoagulant *In Vitro*", J. Infect. Dis. 167:1474-1477 (1993); Seymour, *et al.*, "Ecotin is a Potent Anticoagulant and Reversible Tight-binding Inhibitor of Factor Xa", Biochemistry 33:3949-3958 (1994).

Factor Xa inhibitory compounds which are not large polypeptide-type inhibitors have also been reported including: Tidwell, *et al.*, "Strategies for Anticoagulation With Synthetic Protease Inhibitors. Xa Inhibitors Versus Thrombin Inhibitors", Thromb. Res. 19:339-349 (1980); Turner, *et al.*, "p-Amidino Esters as Irreversible Inhibitors of Factor IXa and Xa and Thrombin", Biochemistry 25:4929-4935 (1986); Hitomi, *et al.*, "Inhibitory Effect of New Synthetic Protease Inhibitor (FUT-175) on the Coagulation System", Haemostasis 15:164-168 (1985); Sturzebecher, *et al.*, "Synthetic Inhibitors of Bovine Factor Xa and Thrombin. Comparison of Their Anticoagulant Efficiency", Thromb. Res. 54:245-252 (1989); Kam, *et al.*, "Mechanism Based Isocoumarin Inhibitors for Trypsin and Blood Coagulation Serine Proteases: New Anticoagulants", Biochemistry 27:2547-2557 (1988); Hauptmann, *et al.*, "Comparison of the Anticoagulant and Antithrombotic Effects of Synthetic Thrombin and Factor Xa Inhibitors", Thromb. Haemost. 63:220-223 (1990); Miyadera, *et al.*, Japanese Patent Application JP 6327488 (1994); Nagahara, *et al.*, "Dibasic (Amidinoaryl)propanoic Acid Derivatives as Novel Blood Coagulation Factor Xa Inhibitors", J. Med. Chem. 37:1200-1207 (1994); Vlasuk, *et al.*, "Inhibitors of Thrombosis" European Patent Application, WO 93/15756 (1993); and Brunck, *et al.*, "Novel Inhibitors of Factor Xa", European Patent Application, WO 94/13693 (1994). Al-obeidi, *et al.*, "Factor Xa Inhibitors", WO patent 95/29189, discloses pentapeptide X1-Y-I-R-X2 derivatives as factor Xa inhibitors. Said compounds are useful for inhibiting blood clotting in the treatment of thrombosis, stroke, and myocardial infarction.

WO 96/18644 to Tamura, *et al.*, describes aromatic heterocyclic thrombin inhibitors. WO 95/35313 to Semple, *et al.*, pertains to 3-amino-2-oxo-1-piperidineacetic derivative thrombin inhibitors.

EP 0,512,831 and US Patent No. 5,281,585, both to Duggan, *et al.*, describe fibrinogen receptor antagonists.

SUMMARY OF THE INVENTION

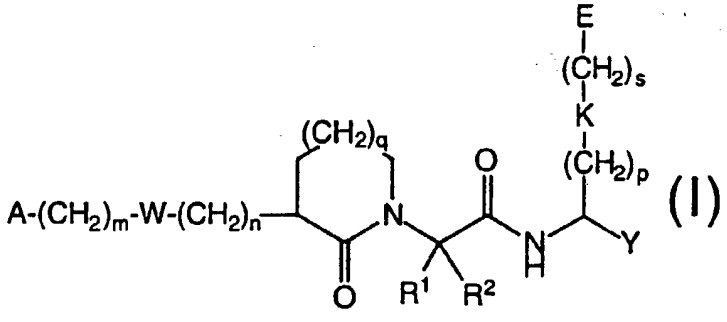
The present invention relates to novel peptide and peptide mimetic analogs, their pharmaceutically acceptable isomers, salts, hydrates, solvates and prodrug derivatives.

In another aspect, the present invention includes pharmaceutical compositions comprising a pharmaceutically effective amount of the compounds of this invention and a pharmaceutically acceptable carrier. These compositions are useful as potent and specific inhibitors of blood coagulation in mammals.

In yet another aspect, the invention relates to methods of using these inhibitors as therapeutic agents for disease states in mammals which have disorders of coagulation such as in the treatment or prevention of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation including the treatment of septic shock, deep venous thrombosis in the prevention of pulmonary embolism or the treatment of reocclusion or restenosis of reperfused coronary arteries. These compositions may optionally include anticoagulants, antiplatelet agents, and thrombolytic agents.

In other aspects of the invention compounds are provided which are useful as diagnostic reagents.

In preferred embodiments, the present invention provides compounds of general formula I:



(I)

Wherein:

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-3}alkylaryl, C_{1-3}alkyl-C_{3-8}cycloalkyl or aryl and R^2 is H, C_{1-6}alkyl, or R^1 and R^2 are taken together to form a carbocyclic ring;

m is an integer from 0-3;

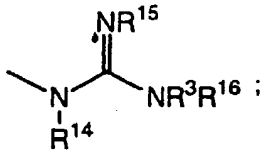
n is an integer from 0-6;

p is an integer from 0-4;

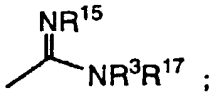
s is an integer from 0-2;

q is an integer from 0-2;

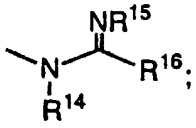
A is selected from the group consisting of: a five to ten membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O and S; R^3; $-NR^3R^4$;



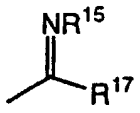
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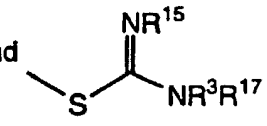
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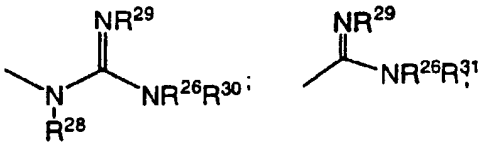


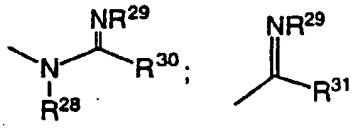
where R^3, R^4, R^{14} and R^{15} are independently selected from the group consisting of H, -OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl; R^{16} is selected from the group consisting of H, -OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl, or can be taken together with R^{14} or R^{15} to form a 5-6 membered ring; and R^{17} is selected from the group consisting of H, -OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl, or can be taken together with R^{15} to form a 5-6 membered ring;

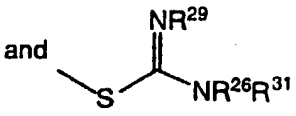
W is C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{1-6}alkenyl, aryl, or a five to ten membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O and S;

K is selected from the group consisting of a direct link, C_{3-8}cycloalkyl, aryl, or a five to ten membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O and S;

E is selected from the group consisting of R^{26}, $-NR^{26}R^{27}$,

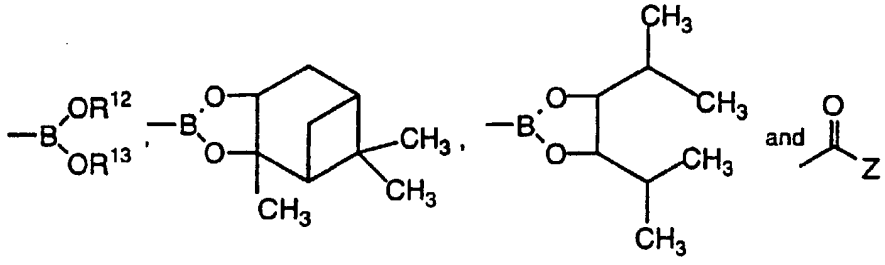




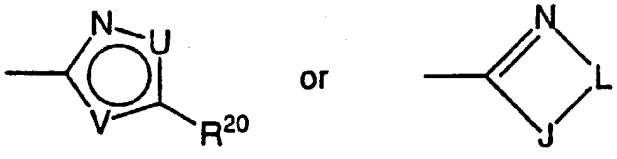


where R^{26}, R^{27}, R^{28} and R^{29} are independently selected from the group consisting of H, -OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl; R^{30} is selected from the group consisting of H, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl, or can be taken together with R^{28} or R^{29} to form a 5-6 membered ring; and R^{31} is selected from the group consisting of H, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl, or can be taken together with R^{29} to form a 5-6 membered ring; with the proviso that when E is R^{26}, then K must contain at least one N atom;

Y is selected from the group consisting of H,



where R^{12} and R^{13} are independently selected from the group consisting of H, C_{1-3}alkyl and aryl; and G is H, $-COOR^{18}$, $-CONR^{18}R^{19}$, $-CF_3$, $-CF_2CF_3$ or a group having the formula:

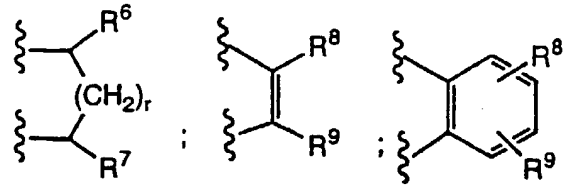


where:

R^{20} is selected from the group consisting of H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{0-6}alkylaryl, C_{2-6}alkenylaryl, C_{0-6}alkylheterocyclo, C_{2-6}alkenylheterocyclo, $-CF_3$ and $-CF_2CF_3$;

J is -S-, -SO-, -SO_2-, -O- or -NR^5-, where R^5 is H, C_{1-6}alkyl or benzyl; and

L is selected from the group consisting of:



and

a C_{6-10} heterocyclic ring system substituted by R^8 and R^9 and containing 1-4 heteroatoms selected from N, S and O; where r is an integer from 0-2; R^6 and R^7 are independently selected from the group consisting of H, C_{1-6}alkyl, aryl, C_{1-6}alkylaryl, -$COOR^{10}$, -$CONR^{10}R^{11}$, -CN and -CF_3; R^8 and R^9 are independently selected from the group consisting of H, C_{1-6}alkyl, aryl, C_{1-6}alkylaryl, C_{1-4}alkyloxy, halogen, -NO_2, -$NR^{10}R^{11}$, -$NR^{10}COR^{11}$, -O-R^{10}, -O-COR^{10}, -$COOR^{10}$, -$CONR^{10}R^{11}$, -CN, -CF_3, -$SO_2NR^{10}R^{11}$ and C_{1-6}alkyl-O-R^{10}; and R^{10} and R^{11} are independently selected from the group consisting of H, C_{1-6}alkyl, C_{1-3}alkylaryl and aryl;

U is -O-, -S-, -N- or -N(H)-; and

V is -O-, -S-, -N- or -N(H)-; with the proviso that at least one of U or V is -N- or -N(H)-;

and all optical isomers thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions

In accordance with the present invention and as used herein, the following terms are defined with the following meanings, unless explicitly stated otherwise.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain, cyclic groups, and combinations thereof, having the number of carbon atoms specified, or if no number is specified, having up to 12 carbon atoms. The term "cycloalkyl" refers to a mono-, bi-, or tricyclic aliphatic ring having 3 to 12 carbon atoms, preferably 3 to 7 carbon atoms.

The term "alkenyl" refers to unsaturated aliphatic groups including straight-chain, branched-chain, cyclic groups, and combinations thereof, having at least one double bond and having the number of carbon atoms specified.

The term "aryl" refers to an unsubstituted or substituted aromatic ring(s), substituted with one, two or three substituents such as, by way of example and not limitation, C_{1-6}alkoxy, C_{1-6} alkyl, C_{1-6} alkylamino, hydroxy, halogen, cyano (-CN), hydroxyl, mercapto, nitro (-NO_2), thioalkoxy, carboxaldehyde, carboxyl, carboalkoxy, carboxamide, -NR'R", -NR'COR", -OR, -OCOR, -COOR, -CONR'R", -CF_3, -SO_2NR'R" and C_{1-6}alkyl-OR; aryl, C_{1-6}alkylaryl (where the R groups can be H, C_{1-6}alkyl, C_{1-3}alkylaryl and aryl), including but not limited to carbocyclic aryl, heterocyclic aryl, biaryl and triaryl groups and the like, all of which may be optionally substituted. Preferred aryl groups include phenyl, halophenyl, C_{1-6}alkylphenyl, naphthyl, biphenyl. phenanthrenyl, naphthacenyl, and aromatic heterocyclics or heteroaryls, the latter of which is an aryl group containing one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. Aryl groups preferably have 5-14 carbon atoms making up the ring(s) structure, while heteroaryls preferably have 1-4 heteroatoms, with the remaining 4-10 atoms being carbon atoms.

The terms "heterocyclo" and "hetero cyclic ring system" as used herein refer to any saturated or unsaturated mono- or bicyclic ring system, containing from one to four heteroatoms, selected from the group consisting of nitrogen, oxygen and sulfur. A typical heterocyclic ring system will have five to ten members, 1-4 of which are heteroatoms. Typical examples of monocyclic ring systems include piperidinyl, pyrrolidinyl, pyridinyl, piperidonyl, pyrrolidonyl and thiazolyl, while examples of bicyclic ring systems include benzimidazolyl, benzothiazolyl and benzoxazolyl, all of which may be substituted.

The term "carbocyclic ring" as used herein refers to any saturated or unsaturated ring containing from three to six carbon atoms.

The terms "alkylaryl" and "alkenylaryl" as used herein refer to an alkyl group or

alkenyl group, respectively, having the number of carbon atoms designated, appended to one, two, or three aryl groups. The term benzyl as used herein refers to $-CH_2-C_6H_5$.

The term "alkoxy" as used herein refers to an alkyl linked to an oxygen atom, such as methoxy, ethoxy, and so forth.

The terms "halogen" as used herein refer to Cl, Br, F or I substituents.

The term "direct link" as used herein refers to a bond directly linking the substituents on each side of the direct link. When two adjacent substituents are defined as each being a "direct link", it is considered to be a single bond.

Two substituents are "taken together to form a 5-6 membered ring" means that an ethylene or a propylene bridge, respectively, is formed between the two substituents.

The term "pharmaceutically acceptable salts" includes salts of compounds derived from the combination of a compound and an organic or inorganic acid. These compounds are useful in both free base and salt form. In practice, the use of the salt form amounts to use of the base form; both acid and base addition salts are within the scope of the present invention.

"Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, and organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid and the like.

"Pharmaceutically acceptable base addition salts" include those derived from inorganic bases such as sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum bases, and the like. Particularly preferred are the ammonium, potassium, sodium, calcium and magnesium salts. Salts derived from pharmaceutically acceptable organic nontoxic bases include salts of primary, secondary,

and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, such as isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, ethanolamine, 2-diethylaminoethanol, trimethamine, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, hydrabamine, choline, betaine, ethylenediamine, glucosamine, methylglucamine, theobromine, purines, piperizine, piperidine, N-ethylpiperidine, polyamine resins and the like. Particularly preferred organic nontoxic bases are isopropylamine, diethylamine, ethanolamine, trimethamine, dicyclohexylamine, choline, and caffeine.

"Biological property" for the purposes herein means an *in vivo* effector or antigenic function or activity that is directly or indirectly performed by a compound of this invention. Effector functions include receptor or ligand binding, any enzyme activity or enzyme modulatory activity, any carrier binding activity, any hormonal activity, any activity in promoting or inhibiting adhesion of cells to an extracellular matrix or cell surface molecules, or any structural role. Antigenic functions include possession of an epitope or antigenic site that is capable of reacting with antibodies raised against it. The biological properties of the compounds of the present invention can be readily characterized by the methods described in Examples 14 and 15 and by such other methods as are well known in the art.

In addition, the following abbreviations are used in this application:

"Boc" refers to t-butoxycarbonyl.

"BOP" refers to benzotriazol-1-yloxy-tris-(dimethylamino) phosphonium hexafluorophosphate.

"DIEA" refers to diisopropylethylamine.

"DMF" refers to N,N-dimethylformamide.

"DMSO" refers to dimethylsulfoxide.

"Et_2O" refers to diethyl ether.

"EtOAc" refers to ethyl acetate.

"HOAc" refers to acetic acid.

"LDA" refers to lithium diisopropylamide.

"MeOH" refers to methanol.

"MeSEt" refers to methyl ethyl sulfide.

"$NaN(TMS)_2$" refers to sodium bis-trimethyl silyl amide.

"TFA" refers to trifluoroacetic acid.

"THF" refers to tetrahydrofuran.

"Tos" refers to p-toluenesulfonyl.

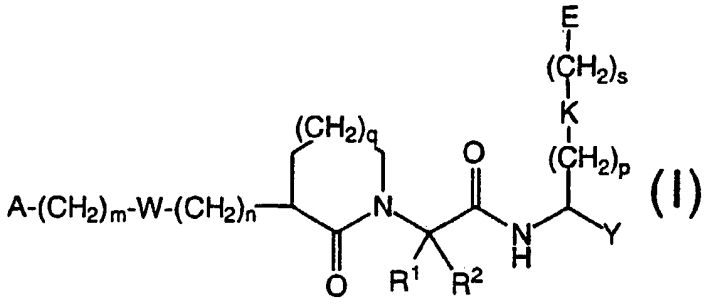
In the compounds of this invention, carbon atoms bonded to four non-identical substituents are asymmetric. Accordingly, the compounds may exist as diastereoisomers, enantiomers or mixtures thereof. The syntheses described herein may employ racemates, enantiomers or diastereomers as starting materials or intermediates. Diastereomeric products resulting from such syntheses may be separated by chromatographic or crystallization methods, or by other methods known in the art. Likewise, enantiomeric product mixtures may be separated using the same techniques or by other methods known in the art. Each of the asymmetric carbon atoms, when present in the compounds of this invention, may be in one of two configurations (R or S) and both are within the scope of the present invention. In the processes described above, the final products may, in some cases, contain a small amount of diastereomeric or enantiomeric products; however, these products do not affect their therapeutic or diagnostic application.

In all of the peptides of the invention, one or more amide linkages (-CO-NH-) may optionally be replaced with another linkage which is an isostere such as $-CH_2NH-$, $-CH_2S-$, $-CH_2-O-$, $-CH_2CH_2-$, -CH=CH- (cis and trans), $-COCH_2-$, $-CH(OH)CH_2-$, $-CH_2SO-$, and $-CH_2SO_2-$. This replacement can be made by methods known in the art. The following references describe preparation of peptide analogs which include these alternative-linking moieties: Spatola, "Peptide Backbone Modifications" (general review) Vega Data, Vol. 1, Issue 3, (March 1983); Spatola, "Chemistry and Biochemistry of Amino Acids, Peptides and Proteins," (general review) B. Weinstein, eds., Marcel Dekker, New York, p. 267 (1983); Morley, Trends Pharm. Sci. (general review) pp. 463-

468 (1980); Hudson, *et al.*, Int. J. Pept. Prot. Res. 14:177-185 (1979) (-CH_2NH-, -CH_2CH_2-); Spatola, *et al.*, Life Sci. 38:1243-1249 (1986) (-CH_2-S); Hann, J. Chem. Soc. Perkin Trans. I pp.307-314 (1982) (-CH=CH-, cis and trans); Almquist, *et al.*, J Med. Chem. 23:1392-1398 (1980) (-$COCH_2$-); Jennings-White, *et al.*, Tetrahedron Lett. 23:2533 (-$COCH_2$-) (1982); Szelke, *et al.*, European Application EP 45665; CA:97:39405 (1982) (-$CH(OH)CH_2$-); Holladay, *et al.*, Tetrahedron Lett 24:4401-4404 (1983) (-$CH(OH)CH_2$-); and Hruby, Life Sci. 31:189-199 (1982) (-CH_2-S-).

Preferred Embodiments

This invention relates to a new class of peptide derivatives selected from those of general formula I which are potent and specific inhibitors of Xa, their pharmaceutically acceptable compositions thereof, and the methods of using them as therapeutic agents for disease states in mammals characterized by abnormal thrombosis:



(I)

Wherein:

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-3}alkylaryl, C_{1-3}alkyl-C_{3-8}cycloalkyl or aryl and R^2 is H, C_{1-6}alkyl, or R^1 and R^2 are taken together to form a carbocyclic ring;

m is an integer from 0-3;

n is an integer from 0-6;

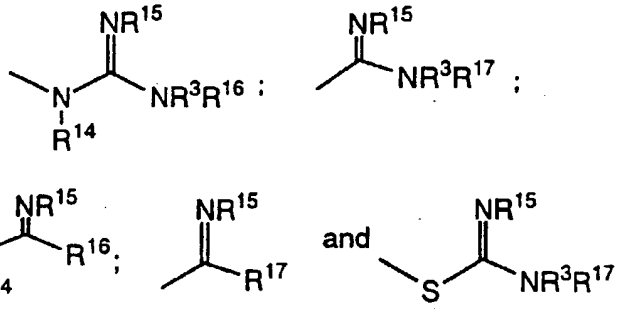
p is an integer from 0-4;

s is an integer from 0-2;

q is an integer from 0-2;

A is selected from the group consisting of: a five to ten membered heterocyclic ring

system containing 1-4 heteroatoms selected from the group consisting of N, O and S; R^3; $-NR^3R^4$;

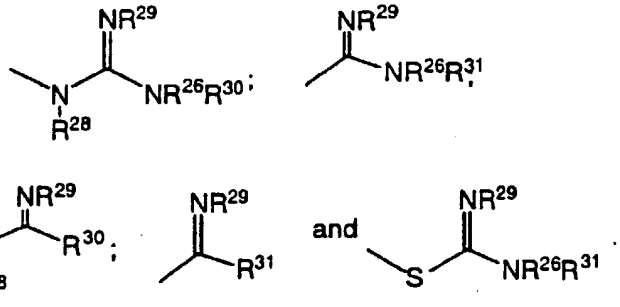


where R^3, R^4, R^{14} and R^{15} are independently selected from the group consisting of H, -OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl; R^{16} is selected from the group consisting of H, -OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl, or can be taken together with R^{14} or R^{15} to form a 5-6 membered ring; and R^{17} is selected from the group consisting of H, -OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl, or can be taken together with R^{15} to form a 5-6 membered ring;

W is C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{1-6}alkenyl, aryl, or a five to ten membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O and S;

K is selected from the group consisting of a direct link, C_{3-8}cycloalkyl, aryl, or a five to ten membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O and S;

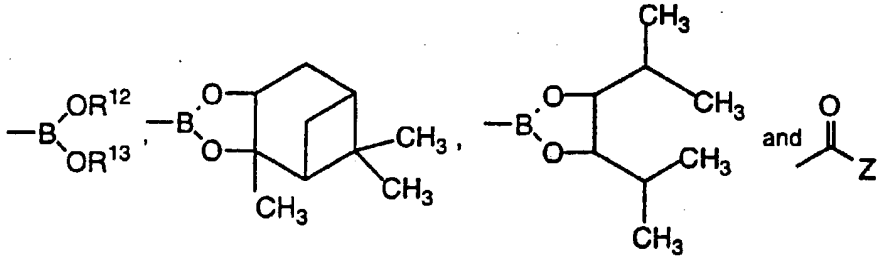
E is selected from the group consisting of R^{26}, $-NR^{26}R^{27}$,



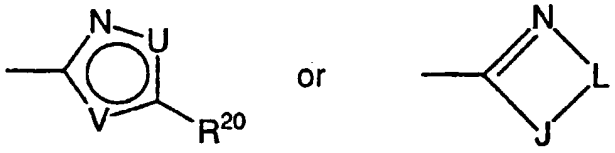
where R^{26}, R^{27}, R^{28} and R^{29} are independently selected from the group consisting of H, -OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl; R^{30} is selected from the group consisting of H,

C_{1-6}alkyl, aryl and C_{1-4}alkylaryl, or can be taken together with R^{28} or R^{29} to form a 5-6 membered ring; and R^{31} is selected from the group consisting of H, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl, or can be taken together with R^{29} to form a 5-6 membered ring; with the proviso that when E is R^{26}, then K must contain at least one N atom;

Y is selected from the group consisting of H,



where R^{12} and R^{13} are independently selected from the group consisting of H, C_{1-3}alkyl and aryl; and G is H, $-COOR^{18}$, $-CONR^{18}R^{19}$, $-CF_3$, $-CF_2CF_3$ or a group having the formula:

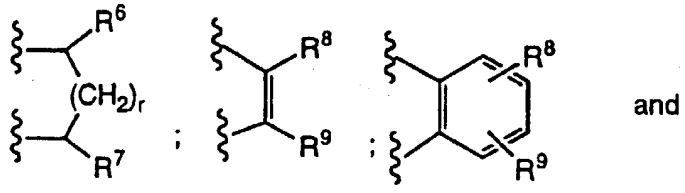


where:

R^{20} is selected from the group consisting of H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{0-6}alkylaryl, C_{2-6}alkenylaryl, C_{0-6}alkylheterocyclo, C_{2-6}alkenylheterocyclo, $-CF_3$ and $-CF_2CF_3$;

J is -S-, -SO-, $-SO_2$-, -O- or $-NR^5$-, where R^5 is H, C_{1-6}alkyl or benzyl; and

L is selected from the group consisting of:



a C_{6-10} heterocyclic ring system substituted by R^8 and R^9 and containing 1-4 heteroatoms selected from N, S and O; where r is an integer from 0-2; R^6 and R^7 are independently selected from the group consisting of H, C_{1-6}alkyl, aryl, C_{1-6}alkylaryl, $-COOR^{10}$,

-$CONR^{10}R^{11}$, -CN and -CF_3; R^8 and R^9 are independently selected from the group consisting of H, C_{1-6}alkyl, aryl, C_{1-6}alkylaryl, C_{1-4}alkyloxy, halogen, -NO_2, -$NR^{10}R^{11}$, -$NR^{10}COR^{11}$, -O-R^{10}, -O-COR^{10}, -$COOR^{10}$, -$CONR^{10}R^{11}$, -CN, -CF_3, -$SO_2NR^{10}R^{11}$ and C_{1-6}alkyl-O-R^{10}; and R^{10} and R^{11} are independently selected from the group consisting of H, C_{1-6}alkyl, C_{1-3}alkylaryl and aryl;

U is -O-, -S-, -N- or -N(H)-; and

V is -O-, -S-, -N- or -N(H)-; with the proviso that at least one of U or V is -N- or -N(H)-;

and all optical isomers thereof.

Preferred R_1 substituents are H and C_{1-6}alkyl; more preferably H.

R^2 is preferably H.

The integer "m" is preferably from 0-1; more preferably 0.

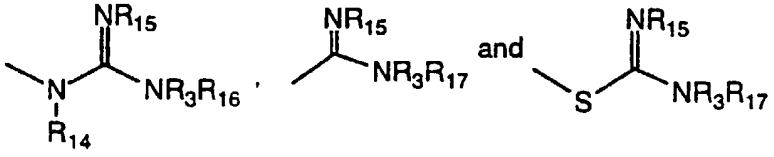
The integer "n" is preferably from 1-4.

The integer "p" is preferably 3.

The integer "s" is preferably 0.

The integer "q" is preferably from 0-1.

Preferred "A" substituents are R^3, -R^3R^4,



R^3 is preferably H, -OH or C_{1-6}alkyl; more preferably H, -OH or methyl.

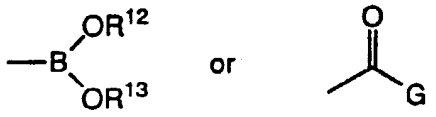
R^4 is preferably H, -OH or C_{1-6}alkyl; more preferably H, -OH or methyl.

Preferred "W" substituents are C_{1-4}alkyl, C_{5-6}cycloalkyl, aryl, or a five to ten membered heterocyclic ring system containing at least one N heteroatom; more preferably C_{1-4}alkyl, aryl, or a five to ten membered heterocyclic ring system containing at least one N heteroatom.

K is preferably a direct link.

In the "E" substituent, it is preferred that R^{26}, R^{27}, R^{28}, R^{29}, R^{30} and R^{31} are independently selected from the group consisting of H and C_{1-6}alkyl, more preferably H and methyl. Particularly preferred "E" substituents are $-NH_2$, $-NHC(=NH)-NH_2$ and $-SC(=NH)-NH_2$; more preferably $-NHC(=NH)-NH_2$ and $-SC(=NH)-NH_2$.

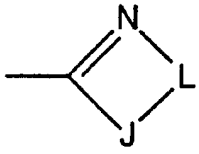
Preferred "Y" substituents are:



R^{12} is preferably H.

R^{13} is preferably H.

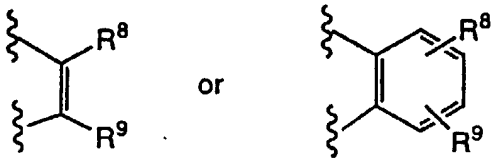
The "G" substituent is preferably a group having the formula:



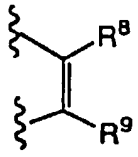
The "J" substituent is preferably -S-, -O- or $-NR^5-$.

R^5 is preferably H.

The "L" substituent is preferably:



more preferably:



R^6 is preferably H.

R^7 is preferably H.

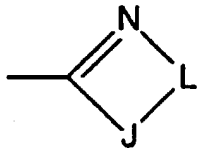
R^8 is preferably H, $-O-R^{10}$, $-COOR^{10}$, $-CONR^{10}R^{11}$ or $-CF_3$; more preferably H.

R^9 is preferably H, -O-R^{10}, -COOR^{10}, -CONR^{10}R^{11} or -CF_3; more preferably H.

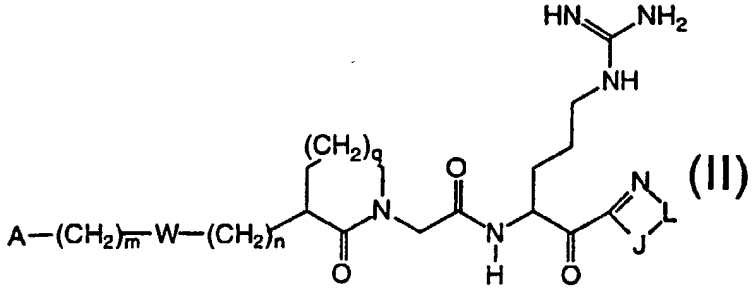
R^{10} is preferably H.

R^{11} is preferably H.

In one embodiment of the invention, R^1 and R^2 are H, p=3, s=0, K is a direct link, E is -NHC(=NH)-NH_2 and Y is -CO-G, where G is a group having the formula:



where J and L are as defined above. This is also illustrated as a preferred group of compounds defined by the general structural formula II as:



(II)

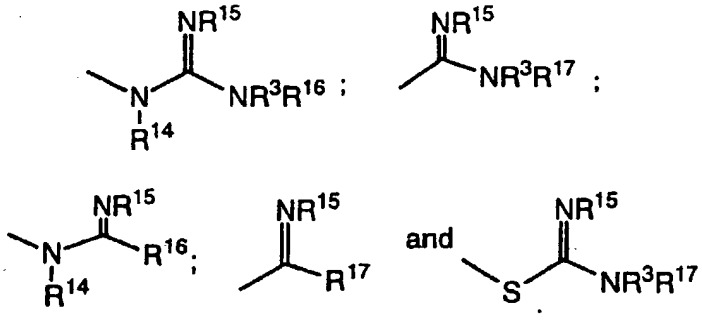
wherein:

m is an integer from 0-3;

n is an integer from 0-6;

q is an integer from 0-2;

A is selected from the group consisting of R^3, -NR^3R^4;



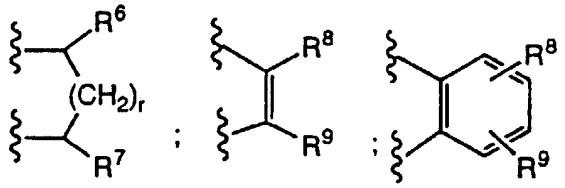
where R^3, R^4, R^{14}, R^{15}, R^{16} and R^{17} are independently selected from the group consisting

of H, -OH and C_{1-6}alkyl;

W is C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{1-6}alkenyl, aryl, or a five to ten membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O and S; with the proviso that when A is R^3, then W must contain at least one N atom;

J is -S-, -SO-, $-SO_2-$, -O- or $-NR^5-$, where R^5 is H; and

L is selected from the group consisting of:

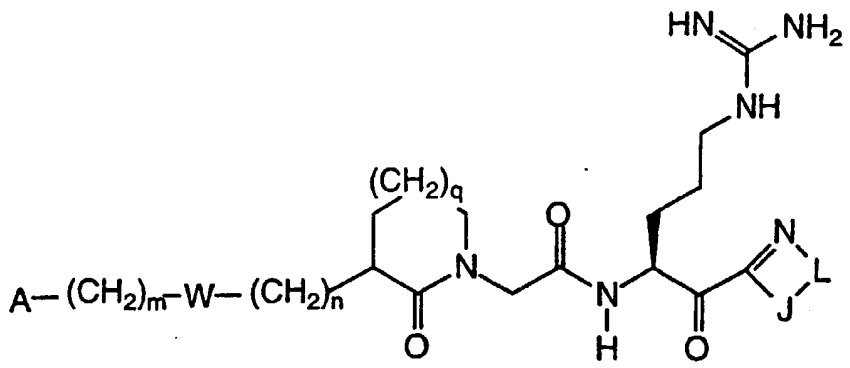


and

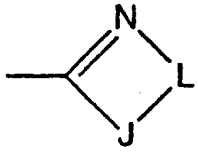
a C_{6-10} heterocyclic ring system substituted by R^8 and R^9 and containing 1-4 heteroatoms selected from N, S and O; where r is an integer from 0-1; R^6 and R^7 are independently selected from the group consisting of H, C_{1-6}alkyl, aryl, C_{1-6}alkylaryl, $-COOR^{10}$, $-CONR^{10}R^{11}$, -CN and $-CF_3$; R^8 and R^9 are independently selected from the group consisting of H, C_{1-6}alkyl, aryl, C_{1-6}alkylaryl, C_{1-4}alkyloxy, halogen, $-NO_2$, $-NR^{10}R^{11}$, $-NR^{10}COR^{11}$, $-O-R^{10}$, $-O-COR^{10}$, $-COOR^{10}$, $-CONR^{10}R^{11}$, -CN, $-CF_3$, $-SO_2NR^{10}R^{11}$ and C_{1-6}alkyl-O-R^{10}; and R^{10} and R^{11} are independently selected from the group consisting of H, C_{1-6}alkyl, C_{1-3}alkylaryl and aryl;

and all optical isomers thereof.

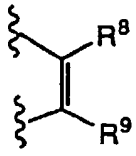
A preferred embodiment of compounds of general formula II have the following stereochemistry:



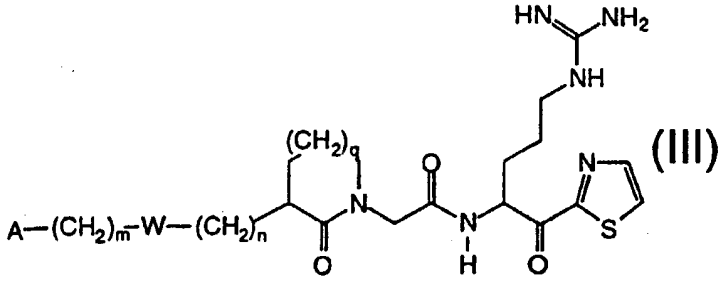
In yet another embodiment of the invention, R^1 and R^2 are H, p=3, s=0, K is a direct link, E is -NHC(=NH)-NH_2, and Y is -CO-G, where G is a group having the formula:



where J is -S- and L is the group:



where R^8 and R^9 are H. This is also illustrated as a preferred group of compounds defined by the general structural formula III as:



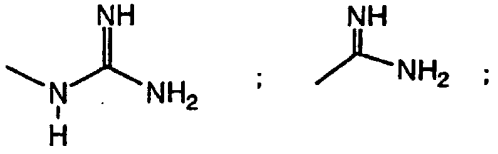
wherein:

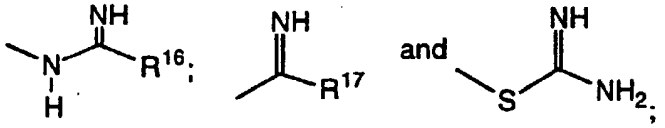
m is an integer from 0-3;

n is an integer from 0-6;

q is an integer from 0-2;

A is selected from the group consisting of R^3, $-NR^3R^4$,



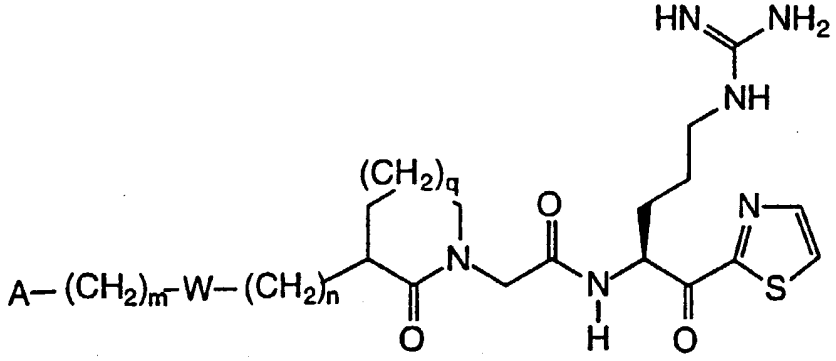


where R^3, R^4, R^{16} and R^{17} are independently selected from the group consisting of H, -OH and C_{1-6}alkyl;

W is C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{1-6}alkenyl, aryl, or a five to ten membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O and S; with the proviso that when A is R^3, then W must contain at least one N atom;

and all optical isomers thereof.

A preferred embodiment of compounds of general formula III have the following stereochemistry:



This invention also encompasses all pharmaceutically acceptable isomers, salts, hydrates and solvates of the compounds of formulas I, II and III. In addition, the compounds of formulas I, II and III can exist in various isomeric and tautomeric forms, and all such forms are meant to be included in the invention, along with pharmaceutically acceptable salts, hydrates and solvates of such isomers and tautomers.

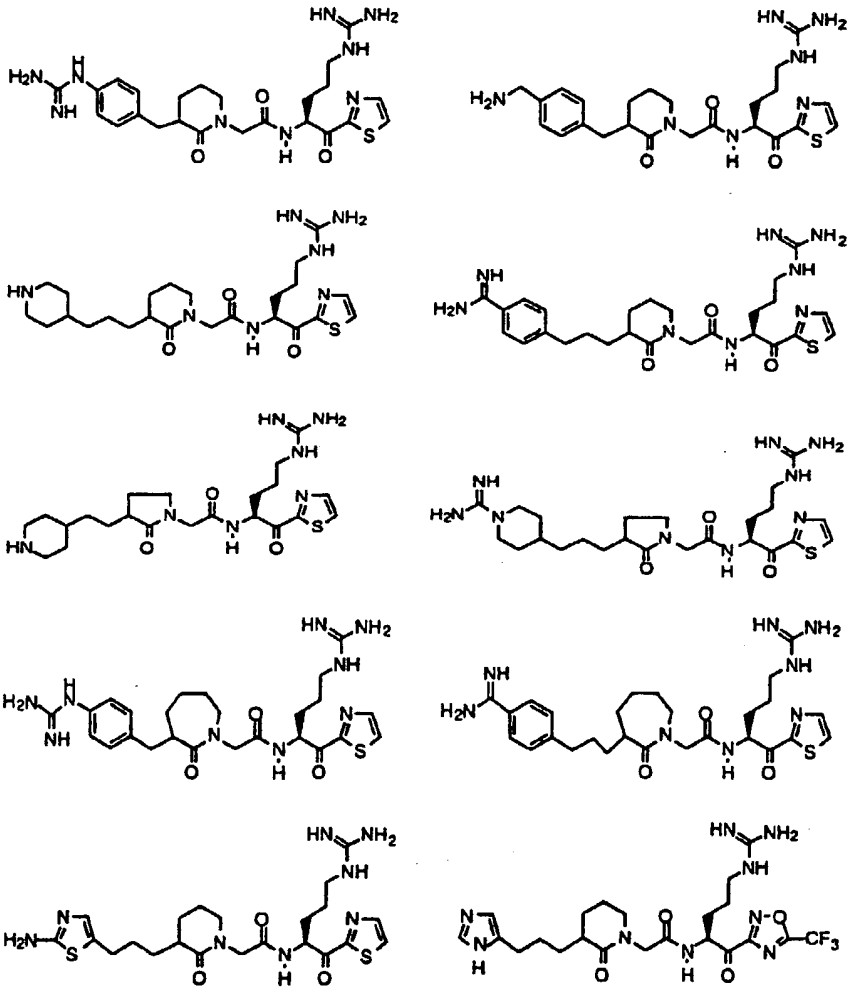
The compounds of this invention may be isolated as the free acid or base or converted to salts of various inorganic and organic acids and bases. Such salts are within the scope of this invention. Non-toxic and physiologically compatible salts are particularly useful although other less desirable salts may have use in the processes of isolation and purification.

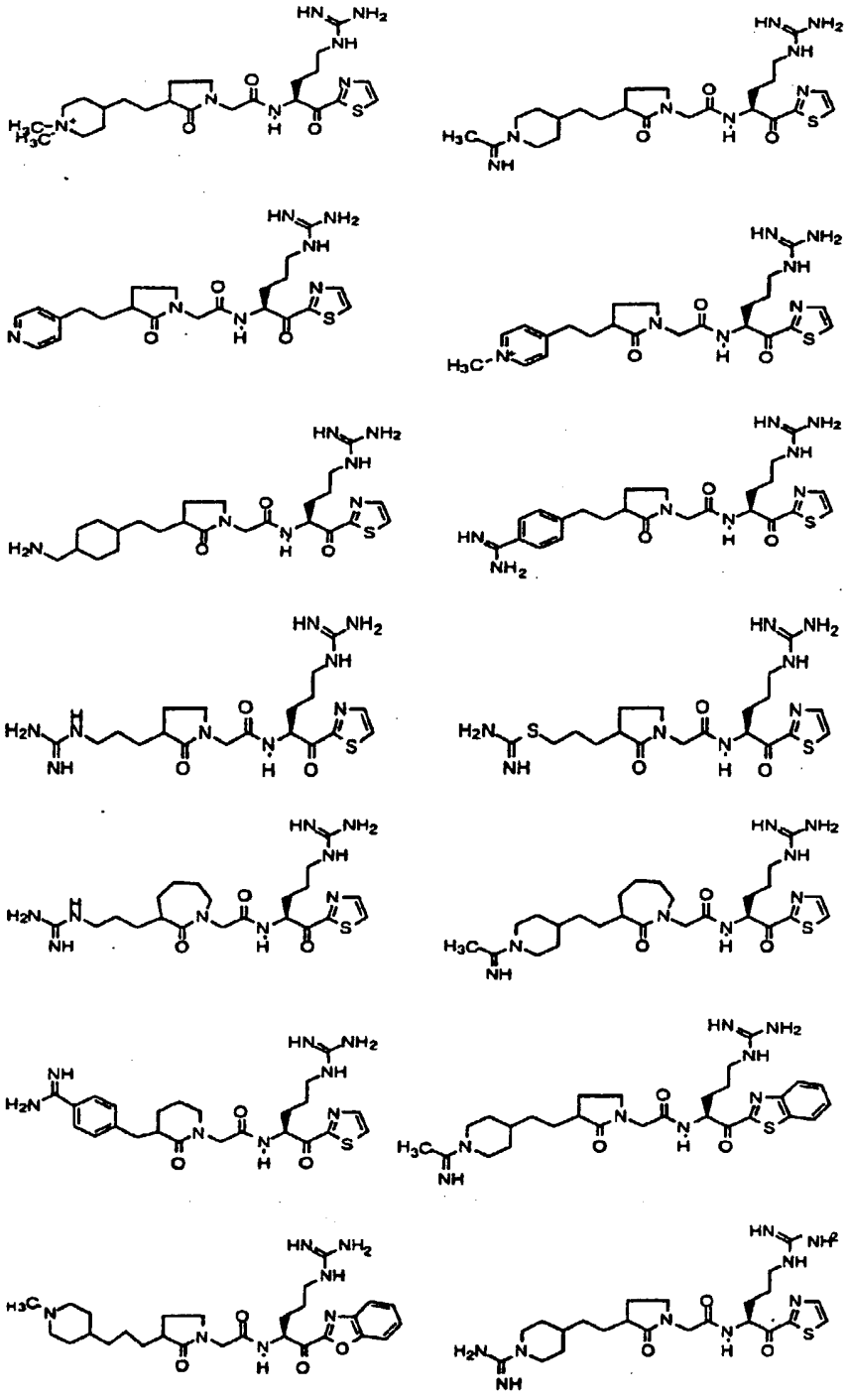
A number of methods are useful for the preparation of the salts described above and are known to those skilled in the art. For example, the free acid or free base form of a compound of one of the formulas above can be reacted with one or more molar equivalents of the desired acid or base in a solvent or solvent mixture in which the salt is insoluble, or in a solvent like water after which the solvent is removed by evaporation, distillation or freeze drying. Alternatively, the free acid or base form of the product may be passed over an ion exchange resin to form the desired salt or one salt form of the product may be converted to another using the same general process.

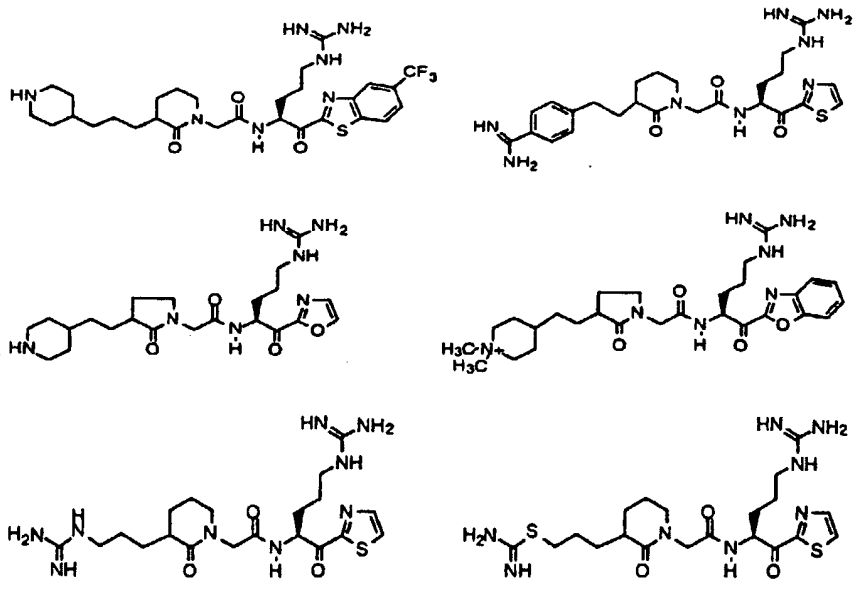
This invention also encompasses prodrug derivatives of the compounds contained herein. The term "prodrug" refers to a pharmacologically inactive derivative of a parent drug molecule that requires biotransformation, either spontaneous or enzymatic, within the organism to release the active drug. Prodrugs are variations or derivatives of the compounds of this invention which have groups cleavable under metabolic conditions. Prodrugs become the compounds of the invention which are pharmaceutically active *in vivo*, when they undergo solvolysis under physiological conditions or undergo enzymatic degradation. Prodrug compounds of this invention may be called single, double, triple etc., depending on the number of biotransformation steps required to release the active drug within the organism, and indicating the number of functionalities present in a precursor-type form. Prodrug forms often offer advantages of solubility, tissue compatibility, or delayed release in the mammalian organism (see, Bundgard, Design of Prodrugs, pp. 7-9, 21-24, Elsevier, Amsterdam 1985 and Silverman, The Organic Chemistry of Drug Design and Drug Action, pp. 352-401, Academic Press, San Diego, CA, 1992). Prodrugs commonly known in the art include acid derivatives well known to

practitioners of the art, such as, for example, esters prepared by reaction of the parent acids with a suitable alcohol, or amides prepared by reaction of the parent acid compound with an amine, or basic groups reacted to form an acylated base derivative. Moreover, the prodrug derivatives of this invention may be combined with other features herein taught to enhance bioavailability.

The following structures are illustrative of the compounds of the present invention and are not intended to be limiting in any manner:







As mentioned above, the compounds of this invention find utility as therapeutic agents for disease states in mammals which have disorders of coagulation such as in the treatment or prevention of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation including the treatment of septic shock, deep venous thrombosis in the prevention of pulmonary embolism or the treatment of reocclusion or restenosis of reperfused coronary arteries. Further, these compounds are useful for the treatment or prophylaxis of those diseases which involve the production and/or action of factor Xa/prothrombinase complex. This includes a number of thrombotic and prothrombotic states in which the coagulation cascade is activated which include but are not limited to, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, thromboembolic complications of surgery and peripheral arterial occlusion.

Accordingly, a method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprises administering to the mammal a therapeutically effective amount of a compound of this invention. In addition to the disease states noted above, other diseases treatable or preventable by the administration

of compounds of this invention include, without limitation, occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty, thrombus formation in the venous vasculature, disseminated intravascular coagulopathy, a condition wherein there is rapid consumption of coagulation factors and systemic coagulation which results in the formation of life-threatening thrombi occurring throughout the microvasculature leading to widespread organ failure, hemorrhagic stroke, renal dialysis, blood oxygenation, and cardiac catheterization.

The compounds of the invention also find utility in a method for inhibiting the coagulation biological samples, which comprises the administration of a compound of the invention.

The compounds of the present invention may also be used in combination with other therapeutic or diagnostic agents. In certain preferred embodiments, the compounds of this invention may be coadministered along with other compounds typically prescribed for these conditions according to generally accepted medical practice such as anticoagulant agents, thrombolytic agents, or other antithrombotics, including platelet aggregation inhibitors, tissue plasminogen activators, urokinase, prourokinase, streptokinase, heparin, aspirin, or warfarin. The compounds of the present invention may act in a synergistic fashion to prevent reocclusion following a successful thrombolytic therapy and/or reduce the time to reperfusion. These compounds may also allow for reduced doses of the thrombolytic agents to be used and therefore minimize potential hemorrhagic side-effects. The compounds of this invention can be utilized *in vivo*, ordinarily in mammals such as primates, (e.g. humans), sheep, horses, cattle, pigs, dogs, cats, rats and mice, or *in vitro*.

The biological properties of the compounds of the present invention can be readily characterized by methods that are well known in the art, for example by the *in vitro* protease activity assays and *in vivo* studies to evaluate antithrombotic efficacy, and effects on hemostasis and hematological parameters, such as are illustrated in the examples.

Diagnostic applications of the compounds of this invention will typically utilize

formulations in the form of solutions or suspensions. In the management of thrombotic disorders the compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration, suppositories, sterile solutions or suspensions or injectable administration, and the like, or incorporated into shaped articles. Subjects in need of treatment (typically mammalian) using the compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from subject to subject and be dependent upon such factors as the type of mammal being treated, its sex, weight, diet, concurrent medication, overall clinical condition, the particular compounds employed, the specific use for which these compounds are employed, and other factors which those skilled in the medical arts will recognize.

Formulations of the compounds of this invention are prepared for storage or administration by mixing the compound having a desired degree of purity with physiologically acceptable carriers, excipients, stabilizers etc., and may be provided in sustained release or timed release formulations. Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical field, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co., (A.R. Gennaro edit. 1985). Such materials are nontoxic to the recipients at the dosages and concentrations employed, and include buffers such as phosphate, citrate, acetate and other organic acid salts, antioxidants such as ascorbic acid, low molecular weight (less than about ten residues) peptides such as polyarginine, proteins, such as serum albumin, gelatin, or immunoglobulins, hydrophilic polymers such as polyvinylpyrrolidinone, amino acids such as glycine, glutamic acid, aspartic acid, or arginine, monosaccharides, disaccharides, and other carbohydrates including cellulose or its derivatives, glucose, mannose or dextrins, chelating agents such as EDTA, sugar alcohols such as mannitol or sorbitol, counterions such as sodium and/or nonionic surfactants such as Tween, Pluronics or polyethyleneglycol.

Dosage formulations of the compounds of this invention to be used for therapeutic

administration must be sterile. Sterility is readily accomplished by filtration through sterile membranes such as 0.2 micron membranes, or by other conventional methods. Formulations typically will be stored in lyophilized form or as an aqueous solution. The pH of the preparations of this invention typically will be 3-11, more preferably 5-9 and most preferably 7-8. It will be understood that use of certain of the foregoing excipients, carriers, or stabilizers will result in the formation of cyclic polypeptide salts. While the preferred route of administration is by injection, other methods of administration are also anticipated such as orally, intravenously (bolus and/or infusion), subcutaneously, intramuscularly, colonically, rectally, nasally, transdermally or intraperitoneally, employing a variety of dosage forms such as suppositories, implanted pellets or small cylinders, aerosols, oral dosage formulations and topical formulations such as ointments, drops and dermal patches. The compounds of this invention are desirably incorporated into shaped articles such as implants which may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers commercially available.

The compounds of the invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of lipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of this invention may also be delivered by the use of antibodies, antibody fragments, growth factors, hormones, or other targeting moieties, to which the compound molecules are coupled. The compounds of this invention may also be coupled with suitable polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidinone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethyl-aspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, compounds of the invention may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic

acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels. Polymers and semipermeable polymer matrices may be formed into shaped articles, such as valves, stents, tubing, prostheses and the like.

Therapeutic compound liquid formulations generally are placed into a container having a sterile access port, for example, an intravenous solution bag or vial having a stopper pierceable by hypodermic injection needle.

Therapeutically effective dosages may be determined by either *in vitro* or *in vivo* methods. For each particular compound of the present invention, individual determinations may be made to determine the optimal dosage required. The range of therapeutically effective dosages will be influenced by the route of administration, the therapeutic objectives and the condition of the patient. For injection by hypodermic needle, it may be assumed the dosage is delivered into the body's fluids. For other routes of administration, the absorption efficiency must be individually determined for each compound by methods well known in pharmacology. Accordingly, it may be necessary for the therapist to titer the dosage and modify the route of administration as required to obtain the optimal therapeutic effect. The determination of effective dosage levels, that is, the dosage levels necessary to achieve the desired result, will be readily determined by one skilled in the art. Typically, applications of compound are commenced at lower dosage levels, with dosage levels being increased until the desired effect is achieved.

The compounds of the invention can be administered orally or parenterally in an effective amount within the dosage range of about 0.1 to 100 mg/kg, preferably about 0.5 to 50 mg/kg and more preferably about 1 to 20 mg/kg on a regimen in a single or 2 to 4 divided daily doses and/or continuous infusion.

Typically, about 5 to 500 mg of a compound or mixture of compounds of this invention, as the free acid or base form or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, excipient, binder, preservative, stabilizer, dye, flavor etc., as called for by accepted pharmaceutical practice.

The amount of active ingredient in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are binders such as acacia, corn starch or gelatin, and excipients such as microcrystalline cellulose, disintegrating agents like corn starch or alginic acid, lubricants such as magnesium stearate, sweetening agents such as sucrose or lactose, or flavoring agents. When a dosage form is a capsule, in addition to the above materials it may also contain liquid carriers such as water, saline, or a fatty oil. Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as an oil or a synthetic fatty vehicle like ethyl oleate, or into a liposome may be desired. Buffers, preservatives, antioxidants and the like can be incorporated according to accepted pharmaceutical practice.

Preparation of the Disclosed Compounds

The compounds of the present invention may be synthesized by either solid or liquid phase methods described and referenced in standard textbooks, or by a combination of both methods. These methods are well known in the art. See, Bodanszky, "The Principles of Peptide Synthesis", Hafner, *et al.*, Eds., Springer-Verlag, Berlin, 1984.

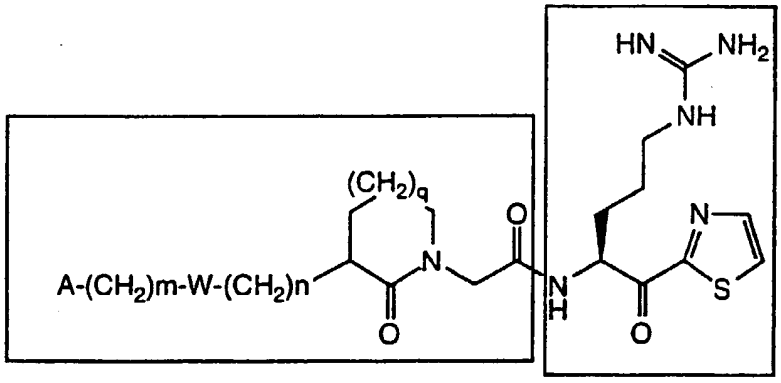
Starting materials used in any of these methods are commercially available from chemical vendors such as Aldrich, Sigma, Nova Biochemicals, Bachem Biosciences, and the like, or may be readily synthesized by known procedures.

Reactions are carried out in standard laboratory glassware and reaction vessels under reaction conditions of standard temperature and pressure, except where otherwise indicated.

During the synthesis of these compounds, the functional groups of the amino acid derivatives used in these methods are protected by blocking groups to prevent cross

reaction during the coupling procedure. Examples of suitable blocking groups and their use are described in "The Peptides: Analysis, Synthesis, Biology", Academic Press, Vol. 3 (Gross, *et al.*, Eds., 1981) and Vol. 9 (1987), the disclosures of which are incorporated herein by reference.

Two exemplary synthesis schemes are outlined directly below, and the specific syntheses are described in the Examples. The reaction products are isolated and purified by conventional methods, typically by solvent extraction into a compatible solvent. The products may be further purified by column chromatography (reversed-phase HPLC) or other appropriate methods.



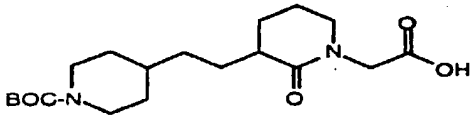
Formula IV

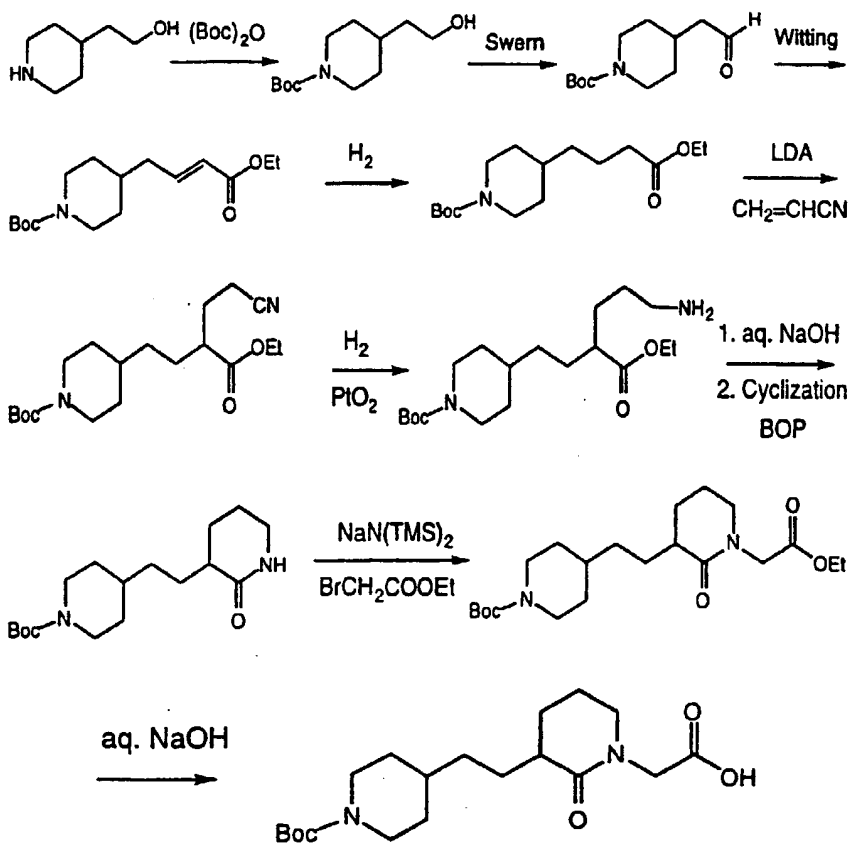
The peptide derivatives can be prepared by coupling of protected Fragment-1 (Scheme 1) to protected Fragment-2 (Scheme 2). The protecting groups are finally removed by HF-cleavage.

Most compounds are purified by reversed-phase HPLC and characterized by ion-spray MS spectrometry

Scheme I

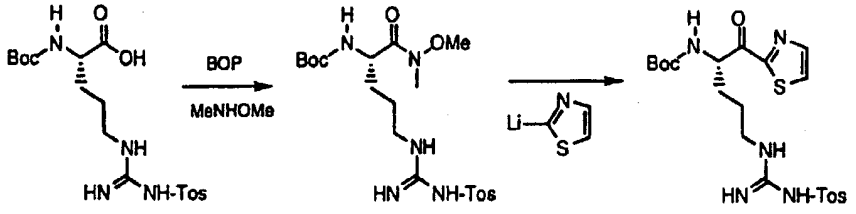
Preparation of Fragment-1

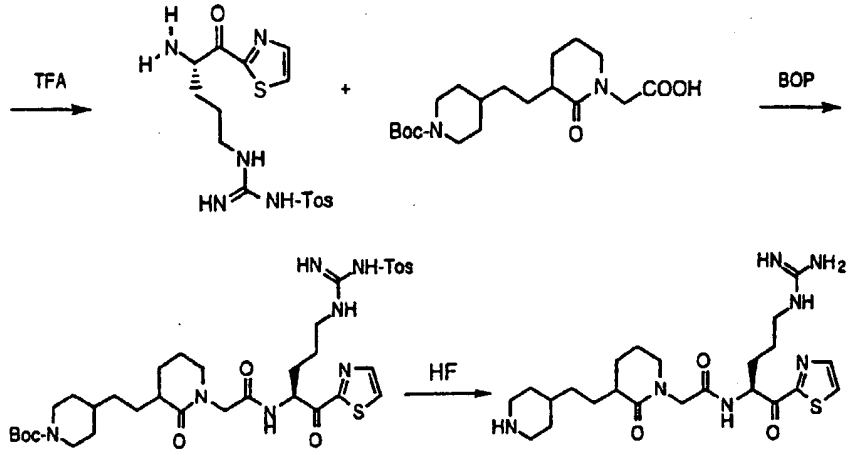




Scheme II

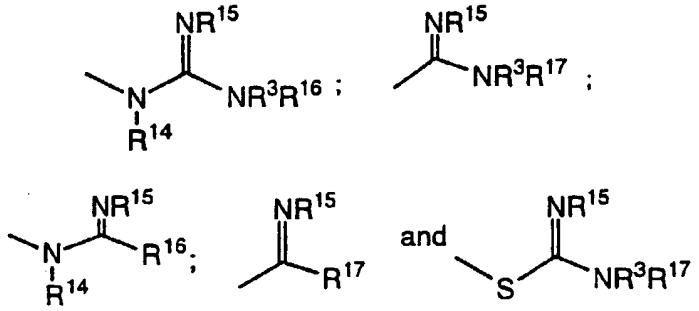
Synthesis of Fragment-2 and Final Inhibitor





The chemical reactions described in Schemes I and II can easily be modified and combined with other techniques that are well known in the art to produce other compounds within the family of formula I.

Methods of incorporating "A" substituents such as R^3, $-NR^3R^4$;



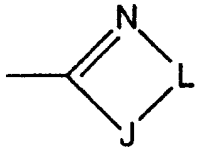
are well known in the art. The chemistry of using the various R substituents (H, -OH, C_{1-6}alkyl and C_{1-4}alkylaryl) is also well known in the art. Methods of incorporating "W" substituents such as C_{1-6}alkyl, C_{3-8}cycloalkyl, aryl, or a five to ten membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O and S, are also well known in the art. In addition, "A" and "W" substituents are illustrated in Example 13.

The "R_1" substituent illustrated in Fragments -1 and -2 is -H. Fragments similar to these structures, where R_1 is C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-3}alkylaryl, or aryl, can easily be synthesized by techniques that are well known in the art. See, for example, Duggan, *et*

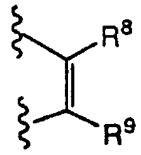
al., U.S. Patent No. 5,281,585.

The "E" substituent illustrated in Fragment-2 (-NHC(=NH)-NH_2) is merely illustrative of one of the various "E" substituents encompassed by the invention. Fragments similar to the structure of Fragment-2, where E is -NH_2, -SC(=NH)-NH_2 or -C(=NH)-NH_2, can easily be synthesized by techniques that are well known in the art.

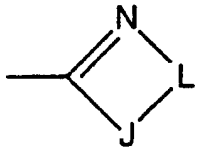
The "Y" substituent illustrated in Fragment-2 is -CO-G, where G is:



where: J is -S- and L is

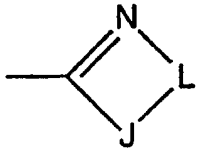


and R^8 and R^9 are H. Fragments similar to the structure of Fragment-2, where G is:

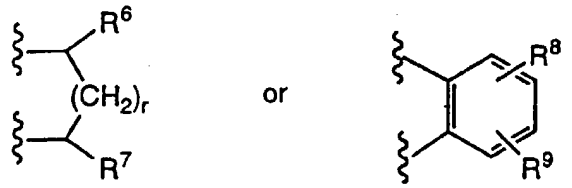


and J is -SO- or -SO_2- can easily be synthesized by techniques that are well known in the art. Fragments where J is -O- can be synthesized by techniques illustrated in J. Am. Chem. Soc. 114: 1854-1863 (1992), J. Med. Chem. 38:76-85 (1995), and J. Med. Chem. 37:3492-3502 (1994). Lastly, fragments where J is -NR^5-, where R^5 is H, C_{1-6}alkyl or benzyl, can be synthesized by techniques illustrated in J. Med. Chem. 37:3492-3502 (1994). All of these references are incorporated herein by reference.

Fragments similar to the structure of Fragment-2, where G is:



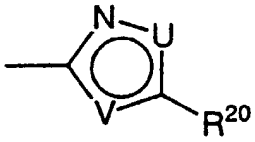
and L is:



where R^6, R^7, R^8 and R^9 are not H, can also be easily synthesized by techniques that are well known in the art.

Fragments similar to the structure of Fragment-2, where G is H, -$COOR^{18}$, -$CONR^{18}R^{19}$, -CF_3 or -CF_2CF_3, can easily be synthesized by techniques that are well known in the art.

Fragments similar to the structure of Fragment-2, where G is:



and U and V are the various substituents (-O-, -S-, -N-, -N(H)-) can also easily be synthesized by well known techniques illustrated in J. Med. Chem. 38: 1355-1371 (1995) and J. Med. Chem. 37: 2421-2436 (1994).

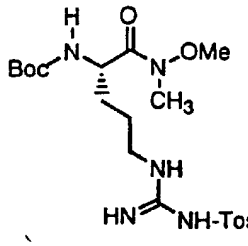
Fragments similar to the structure of Fragment-2, where "Y" is a boron-containing group can easily be synthesized by techniques that are well known in the art. See for example, J. Org. Chem. 60:3717-3722 (1995).

The mechanisms for coupling the fragments used to synthesize the compounds of the instant invention, are also well known in the art.

Without further elaboration, it is believed that one skilled in the art can utilized the present invention to its fullest extent. Therefore, the following preferred specific embodiments are to be construed as merely illustrative and do not limit the remainder of the disclosure in any way whatsoever.

EXAMPLE 1

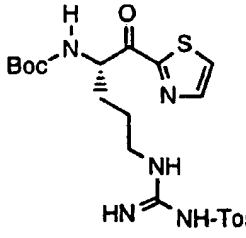
Preparation of Boc-Arg(Tos)-N(Me)OMe



To a suspension of Boc-Arg(Tos)-OH (2 g, 4.7 mmol) in DMF (20 mL) at 0°C is added MeNHOMe.HCl (1 g, 10.3 mmol), DIEA (6 mL) and BOP (2.5 g, 5.6 mmol). The solution is stirred at 0°C for 10 h. DMF is evaporated by vacuum. The oily residue is dissolved in EtOAc (200 mL) and water (20 mL). The organic layer is washed with sat. NaHCO3, water (20 mL), 1 M HCl (10 mL) and sat. NaCl (2 X 20 mL). The organic layer is dried over $MgSO_4$, filtered and evaporated to give a suspension. The suspension is filtered, washed with cold EtOAc (10 mL) and dried to give Boc-Arg(Tos)-N(Me)OMe (1.5 g, 70 % yield). FAB-MS (M+H)+ = 472

EXAMPLE 2

Preparation of Boc-Arg(Tos)-Thiazole

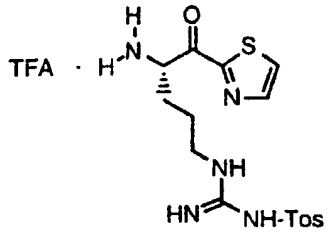


To a solution of thiazole (2.5 g, 29 mmol) in THF (25 mL) at -78°C is added n-BuLi (1.6 M in hexane, 19 mL) dropwise. The mixture is stirred for 30 min. Then a solution of Boc-Arg(Tos)-N(Me)OMe (1.7 g, 3.6 mmol) in THF (50 mL) is added to the lithiothiazole mixture at -78°C. The solution is stirred for 2 h. 1M HCl (30 mL) is added to the reaction mixture and warmed to room temperature. The mixture is extracted with EtOAc (100 mL). The organic layer is washed with sat. NaCl (30 mL), dried over

$MgSO_4$, filtered and evaporated. The crude oily residue is purified by flash column over SiO_2 (50% EtOAc in CH_2Cl_2) to give Boc-Arg(Tos)-Thiazole (1.5 g, 84% yield) as a powder. DCI -MS $(M+H)^+ = 496$

EXAMPLE 3

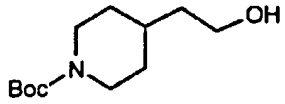
Preparation of H-Arg(Tos)-Thiazole



To a solution of Boc-Arg(Tos)-Thiazole (300 mg, 0.6 mmol) in CH_2Cl_2 (10 mL) at 0°C is added TFA (10 mL). The solution is stirred at 0°C for 2 h. The solvent and excess TFA are evaporated to an oily residue which is used directly without further purification.

EXAMPLE 4

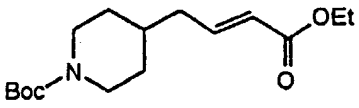
Preparation of N-Boc-4-piperidineethanol



A stirred solution of 4-piperidineethanol (1.87 g, 14 mmol) and DMF (5 mL) at 0°C is treated with N-t-butoxycarbonyl anhydride (3 g, 14 mmol). After 1 h, the cooling bath is removed and the reaction mixture stirred for an additional 20 h. The reaction mixture is then diluted with ether, and concentrated to furnish the title compound (2.6 g, 82%) as a colorless oil.

EXAMPLE 5

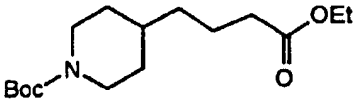
Preparation of Ethyl 4-(N-Boc-piperidin-4-yl)-trans-crotonate



To a stirred solution of oxalyl chloride (0.43 mL, 5.0 mmol) in CH_2Cl_2 (30 mL) at -78°C is added DMSO (0.52 mL, 7.0 mmol) dropwise. After gas evolution subsided (5 min), the alcohol of Example 4 (0.8 g, 3.5 mmol) in CH_2Cl_2 (20 mL) is added in a stream. After 20 min, (carbethoxymethylene) triphenyl-phosphorane (1.4 g, 4.0 mmol) is added. After 2 h, the reaction mixture is diluted with petroleum ether, washed with water, 5% $KHSO_4$ and sat. NaCl, dried over $MgSO_4$, and concentrated. Flash column chromatography (15% EtOAc in hexane) gave the title compound (0.57 g, 38%) as a colorless oil.

EXAMPLE 6

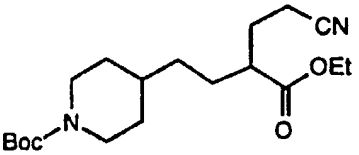
Preparation of Ethyl 4-(N-Boc-piperdin-4-yl)butyrate



The olefin of Example 5 (2.6 g, 8.7 mmol) in EtOAc (50 mL) at room temperature is stirred under a hydrogen atmosphere (1 atm) in the presence of 10% Pd/C (500 mg) overnight. The reaction mixture is then purged with argon, followed by filtration through a Celite pad. Concentration of the filtrate followed by flash chromatography (10% EtOAc in hexane) gave the title ester (2.4 g, 92%) as a crystalline solid.

EXAMPLE 7

Preparation of:

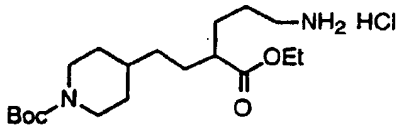


To a solution of $TiCl_4$ (4.2 mL, 4.2 mmol, 1 M in CH_2Cl_2) and CH_2Cl_2 (25 mL) at 0°C

is added titanium isopropoxide (0.42 mL, 1.4 mmol). After 15 min, diisopropylethylamine (1 mL, 6.3 mmol) is added dropwise to form a solution. After 10 min, the ester of Example 6 (5 mmol) in CH_2Cl_2 (7 mL) is added, followed by stirring at 0°C for 1 h. Acrylonitrile (3.3 mL, 50 mmol) is added dropwise at 0°C to the solution. After 4 h, the reaction is quenched with sat. NH_4Cl (15 mL) at 0°C and then the mixture extracted with CH_2Cl_2. The combined organic extracts are washed with sat. $NaHCO_3$ and sat. NaCl, dried over $MgSO_4$, and concentrated. Flash column chromatography gives the compound shown above, as an oil.

EXAMPLE 8

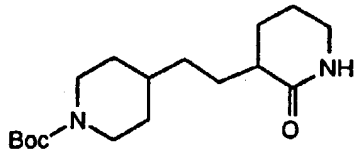
Preparation of:



A mixture of the compound of Example 7 (40 mmol), PtO_2 (2.0 g), MeOH (70 mL) and $CHCl_3$ (7 mL) is shaken on the Parr apparatus under a hydrogen atmosphere (60 psi) at room temperature for 3 h. The reaction mixture is filtered through a Celite pad and concentrated to furnish the crude amine HCl as a solid.

EXAMPLE 9

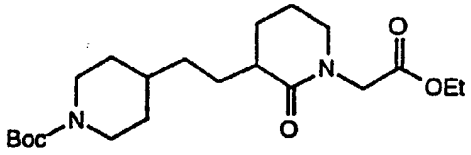
Preparation of:



The crude amine.HCl of Example 8 (10 mmol), acetonitrile (75 mL), and $NaHCO_3$ (3 g) is stirred at room temperature for 20 h. The heterogeneous mixture is then filtered and filtrate concentrated. Flash chromatography gives the compound shown above, as a powder.

EXAMPLE 10

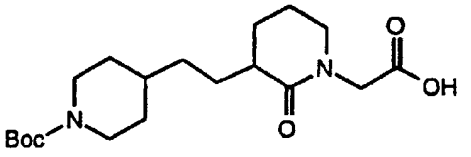
Preparation of:



To a stirred solution of the title compound of Example 9 (6 g, 22 mmol) and THF (15 mL) at -78°C is added $NaN(TMS)_2$ (24.5 mL, 24.5 mmol, 1 M in hexane) dropwise. After 15 min, ethyl bromoacetate (5.2 mL, 45 mmol) is added and then the reaction mixture warmed to 0°C for 1 h. The reaction is quenched with HOAc (1.0 mL) and then the mixture diluted with EtOAc, washed with water and sat. NaCl, dried over $MgSO_4$, and concentrated. Flash chromatography (40% EtOAc in hexane) gave the compound shown above (7.6 g, 78%), as an oil.

EXAMPLE 11

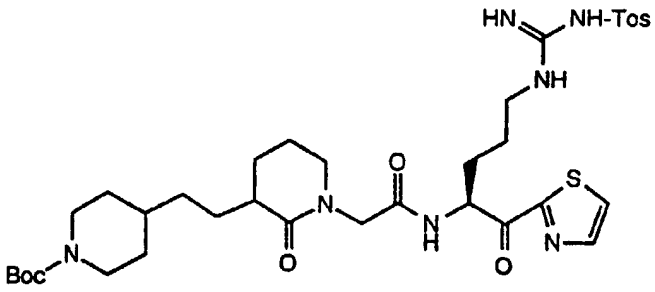
Preparation of:



A solution of the compound of Example 10 (6.0 g, 15 mmol), 1N NaOH (50 mL, 50 mmol), and MeOH (75 mL) is stirred at room temperature for 1 h. The reaction mixture is then acidified with 5% $KHSO_4$ and then extracted with EtOAc. The organic portion is washed with sat. NaCl, dried over $MgSO_4$, and concentrated to give the compound shown above (5.6 g, 100%), as an oil.

EXAMPLE 12

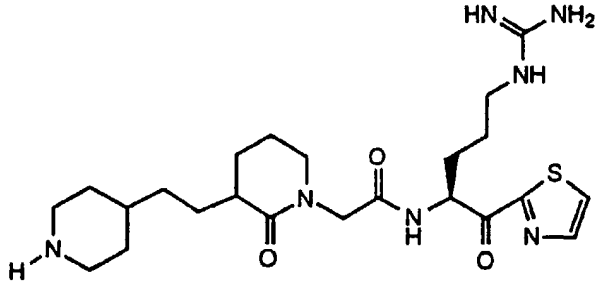
Preparation of:



The compounds of Example 11 (1 mmol) and Example 3 (1 mmol) are dissolved in DMF (5 mL) and cooled to 0°C. The solution is neutralized with DIEA (1 mL) followed by the addition of coupling reagent BOP (1.1 mmol). The solution is stirred for 1-2 h and HPLC analysis shows the completion of reaction. Solvent is removed by vacuum at 30°C. The residue is dissolved in a mixture of EtOAc-H_2O (50 mL:10 mL) and aqueous layer is discarded. The organic layer is washed with sat. $NaHCO_3$ (2 X 10 mL), sat. NaCl (2 X 10 mL), dried over $MgSO_4$, filtered and evaporated. The oil residue is purified by flash column on SiO_2 to give the compound shown above, as a powder.

EXAMPLE 13

Preparation of:



100 mg of the compound of Example 12, 1 ml of anisole and 4 drops of MeSEt are placed in HF-cleavage vessel and cooled under liquid N_2. 10 ml of HF is then condensed and the mixture is stirred at 0°C for 1.25 h. HF is removed under vacuum to give a gum-like residue. The residue is triturated with 20 ml of 50% Et_2O-hexane and the solvent removed by filtration. The gum residue is dissolved in 30 ml of 30% aq. HOAc and filtered through the above sintered funnel. The filtrate is lyophilized to give a powder

which is purified by RP-HPLC to give the compound shown above, as a powder.

EXAMPLE 14 (Determination of IC_{50})

The compounds of the present invention are first dissolved in a buffer to give solutions containing concentrations such that assay concentrations range from 0-100 μM. In assays for thrombin, prothrombinase and factor Xa, a synthetic chromogenic substrate would be added to a solution containing a test compound and the enzyme of interest and the residual catalytic activity of that enzyme would then be determined spectrophotometrically.

The IC_{50} of a compound is determined from the substrate turnover. The IC_{50} is the concentration of test compound giving 50% inhibition of the substrate turnover. Preferred compounds of the invention desirably have an IC_{50} of less than 500 nM in the factor Xa assay, preferably less than 200 nM, and more preferably less than 100 nM. Preferred compounds of the invention desirably have an IC_{50} of less than 4.0 μM in the prothrombinase assay, preferably less than 200 nM, and more preferably less than 10 nM. Preferred compounds of the invention desirably have an IC_{50} of greater than 1.0 μM in the thrombin assay, preferably greater than 10.0 μM, and more preferably greater than 100.0 μM.

Amidolytic Assays for determining protease inhibition activity

Factor Xa and thrombin assays are performed at room temperature, in 0.02 M Tris HCl buffer, pH 7.5, containing 0.15 M NaCl. The rates of hydrolysis of the para-nitroanilide substrate S-2765 (Chromogenix) for factor Xa, and the substrate Chromozym TH (Boehringer Mannheim) for thrombin following preincubation of the enzyme with the test compound for 5 minutes at room temperature are determined using a Softmax 96-well plate reader (Molecular Devices), monitored at 405 nm to measure the time dependent appearance of p-nitroanilide.

The prothrombinase inhibition assay is performed in a plasma free system with modifications to the method as described by Sinha, *et al.*, Thromb. Res., 75:427-436

(1994). The activity of the prothrombinase complex is determined by measuring the time course of thrombin generation using the p-nitroanilide substrate Chromozym TH. The assay consists of a 5 minute preincubation of selected compounds to be tested as inhibitors with the complex formed from factor Xa (0.5 nM), factor Va (2 nM), phosphatidyl serine:phosphatidyl choline (25:75, 20 μM) in 20 mM Tris HCl buffer, pH 7.5, containing 0.15 M NaCl, 5 mM $CaCl_2$ and 0.1% bovine serum albumin. Aliquots from the complex-test compound mixture are added to prothrombin (1 nM) and Chromozym TH (0.1 mM). The rate of substrate cleavage is monitored at 405 nm for two minutes. Several concentrations of a given test compound are assayed in duplicate. A standard curve of thrombin generation by an equivalent amount of untreated complex is then used for determination of percent inhibition.

EXAMPLE 15

The antithrombotic efficacy of the compounds of this invention can readily be evaluated using a series of studies in rabbits, as described below. These studies are also useful in evaluating a compounds effects on hemostasis and its the hematological parameters.

Antithrombotic Efficacy in a Rabbit Model of Venous Thrombosis

A rabbit deep vein thrombosis model as described by Hollenbach, *et al.*, Thromb. Haemost. 71:357-362 (1994), is used to determine the *in vivo* antithrombotic activity of the compounds of the present invention. Rabbits are anesthetized with I.M. injections of Ketamine, Xylazine, and Acepromazine cocktail.

A standardized protocol consists of insertion of a thrombogenic cotton thread and copper wire apparatus into the abdominal vena cava of the anesthetized rabbit. A non-occlusive thrombus is allowed to develop in the central venous circulation and inhibition of thrombus growth is then used as a measure of the antithrombotic activity of the compound being evaluated. Test agents or control saline are administered through a marginal ear vein catheter. A femoral vein catheter is used for blood sampling prior to and

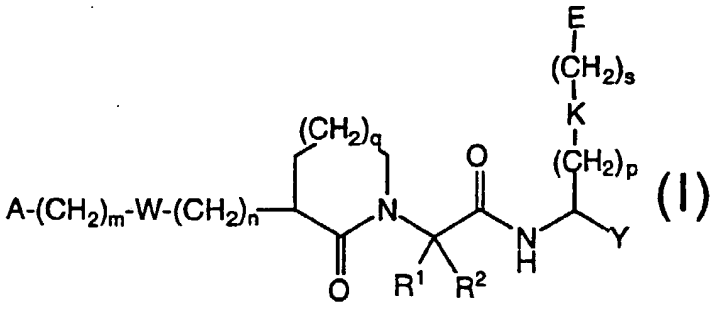
during steady state infusion of the compound being evaluated. Initiation of thrombus formation will begin immediately after advancement of the cotton thread apparatus into the central venous circulation. The compounds being evaluated are administered from time=30 minutes to time=150 minutes at which point the experiment is terminated. The rabbits are euthanized and the thrombus excised by surgical dissection and characterized by weight and histology. Blood samples are then analyzed for changes in hematological and coagulation parameters.

Although the invention has been described with reference to the disclosed embodiments, those skilled in the art will readily appreciate that the specific experiments detailed are only illustrative of the invention. It should be understood that various modifications can be made without departing from the spirit of the invention. Accordingly, the invention is limited only by the following claims.

CLAIMS

What is claimed is:

1. A compound having the formula:



(I)

wherein:

R^1 is H, C_{1-6}alkyl, C_{3-6}cycloalkyl, C_{1-3}alkylaryl, C_{1-3}alkyl-C_{3-8}cycloalkyl or aryl and R^2 is H, C_{1-6}alkyl, or R^1 and R^2 are taken together to form a carbocyclic ring;

m is an integer from 0-3;

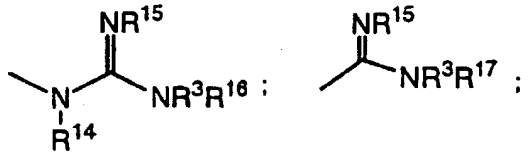
n is an integer from 0-6;

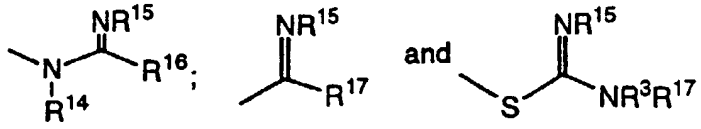
p is an integer from 0-4;

s is an integer from 0-2;

q is an integer from 0-2;

A is selected from the group consisting of: a five to ten membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O and S; R^3; $-NR^3R^4$;





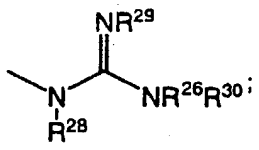
where R^3, R^4, R^{14} and R^{15} are independently selected from the group consisting of H,

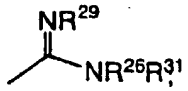
-OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl; R^{16} is selected from the group consisting of H, -OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl, or can be taken together with R^{14} or R^{15} to form a 5-6 membered ring; and R^{17} is selected from the group consisting of H, -OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl, or can be taken together with R^{15} to form a 5-6 membered ring;

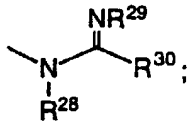
W is C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{1-6}alkenyl, aryl, or a five to ten membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O and S;

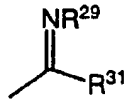
K is selected from the group consisting of a direct link, C_{3-8}cycloalkyl, aryl, or a five to ten membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O and S;

E is selected from the group consisting of R^{26}, $-NR^{26}R^{27}$,

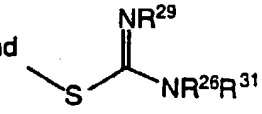






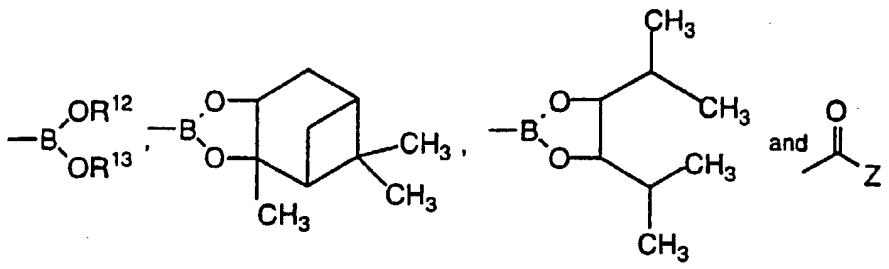


and

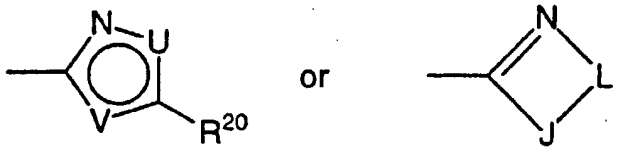


where R^{26}, R^{27}, R^{28} and R^{29} are independently selected from the group consisting of H, -OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl; R^{30} is selected from the group consisting of H, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl, or can be taken together with R^{28} or R^{29} to form a 5-6 membered ring; and R^{31} is selected from the group consisting of H, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl, or can be taken together with R^{29} to form a 5-6 membered ring; with the proviso that when E is R^{26}, then K must contain at least one N atom;

Y is selected from the group consisting of H,



where R^{12} and R^{13} are independently selected from the group consisting of H, C_{1-3}alkyl and aryl; and G is H, $-COOR^{18}$, $-CONR^{18}R^{19}$, $-CF_3$, $-CF_2CF_3$ or a group having the formula:

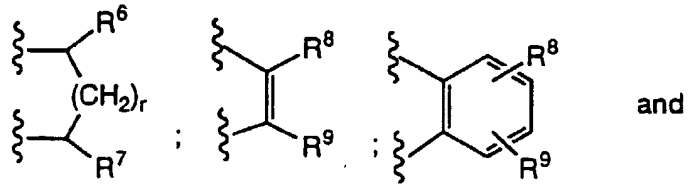


where:

R^{20} is selected from the group consisting of H, C_{1-6}alkyl, C_{2-6}alkenyl, C_{0-6}alkylaryl, C_{2-6}alkenylaryl, C_{0-6}alkylheterocyclo, C_{2-6}alkenylheterocyclo, $-CF_3$ and $-CF_2CF_3$;

J is -S-, -SO-, $-SO_2$-, -O- or $-NR^5$-, where R^5 is H, C_{1-6}alkyl or benzyl; and

L is selected from the group consisting of:



a C_{6-10} heterocyclic ring system substituted by R^8 and R^9 and containing 1-4 heteroatoms selected from N, S and O; where r is an integer from 0-2; R^6 and R^7 are independently selected from the group consisting of H, C_{1-6}alkyl, aryl, C_{1-6}alkylaryl, $-COOR^{10}$, $-CONR^{10}R^{11}$, -CN and $-CF_3$; R^8 and R^9 are independently selected from the group consisting of H, C_{1-6}alkyl, aryl, C_{1-6}alkylaryl, C_{1-4}alkyloxy, halogen, $-NO_2$, $-NR^{10}R^{11}$, $-NR^{10}COR^{11}$, $-O-R^{10}$, $-O-COR^{10}$, $-COOR^{10}$, $-CONR^{10}R^{11}$, -CN, $-CF_3$, $-SO_2NR^{10}R^{11}$ and C_{1-6}alkyl-O-R^{10}; and R^{10} and R^{11} are independently selected from the group consisting of H, C_{1-6}alkyl, C_{1-3}alkylaryl and aryl;

U is -O-, -S-, -N- or -N(H)-; and

V is -O-, -S-, -N- or -N(H)-; with the proviso that at least one of U or V is -N- or -N(H)-;

and all optical isomers thereof.

2. The compound of Claim 1 where R_1 is H or C_{1-6}alkyl

3. the compound of Claim 1 where R^2 is H.

4. The compound of Claim 1 where m is an integer from 0-1.

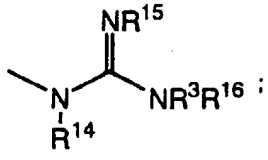
5. The compound of Claim 1 where n is an integer from 1-4.

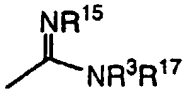
6. The compound of Claim 1 where p is 3.

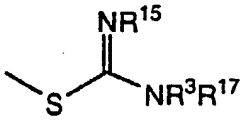
7. The compound of Claim 1 where s is 0.

8. The compound of Claim 1 where q is an integer from 0-1.

9. The compound of Claim 1 where A is selected from the group consisting of R^3; $-NR^3R^4$,



;


and


10. The compound of Claim 9 where R^3 is H, -OH or C_{1-6}alkyl.

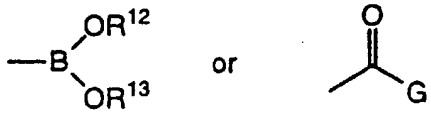
11. The compound of Claim 9 where R^4 is H, -OH or C_{1-6}alkyl.

12. The compound of Claim 1 where W is C_{1-4}alkyl, C_{5-6}cycloalkyl, aryl, or a five to ten membered heterocyclic ring system containing at least one N heteroatom.

13. The compound of Claim 1 where K is a direct link.

14. The compound of Claim 1 where E is $-NH_2$, $-NHC(=NH)-NH_2$ or $-SC(=NH)-NH_2$.

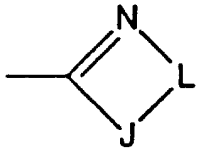
15. The compound of Claim 1 where Y is:



16. The compound of Claim 15 where R^{12} is H.

17. The compound of Claim 15 where R^{13} is H.

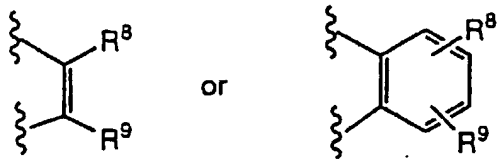
18. The compound of Claim 15 where G is a group having the formula:



19. The compound of Claim 18 where J is -S-, -O- or $-NR^5-$.

20. The compound of Claim 19 where R^5 is H.

21. The compound of Claim 18 where L is:



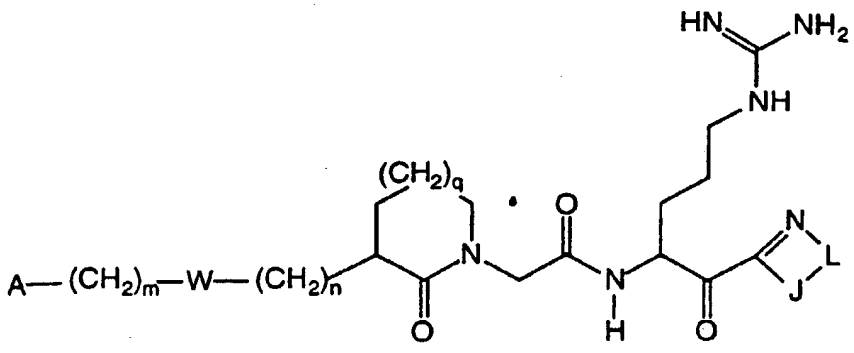
22. The compound of Claim 21 where R^8 is H, -O-R^{10}, -COOR^{10}, -CONR^{10}R^{11} or -CF_3.

23. The compound of Claim 21 where R^9 is H, -O-R^{10}, -COOR^{10}, -CONR^{10}R^{11} or -CF_3.

24. The compound of Claim 1 where R^{10} is H.

25. The compound of Claim 1 where R^{11} is H.

26. A compound having the formula:



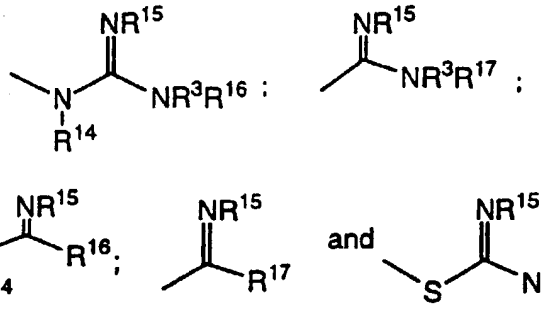
wherein:

m is an integer from 0-3;

n is an integer from 0-6;

q is an integer from 0-2;

A is selected from the group consisting of R^3; -N$R^3$$R^4$;

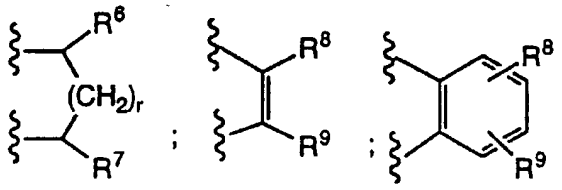


where R^3, R^4, R^{14} and R^{15} are independently selected from the group consisting of H, -OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl; R^{16} is selected from the group consisting of H, -OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl, or can be taken together with R^{14} or R^{15} to form a 5-6 membered ring; and R^{17} is selected from the group consisting of H, -OH, C_{1-6}alkyl, aryl and C_{1-4}alkylaryl, or can be taken together with R^{15} to form a 5-6 membered ring;

W is C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{1-6}alkenyl, aryl, or a five to ten membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O and S; with the proviso that when A is R^3, then W must contain at least one N atom;

J is -S-, -SO-, -SO_2-, -O- or -NR^5-, where R^5 is H; and

L is selected from the group consisting of:



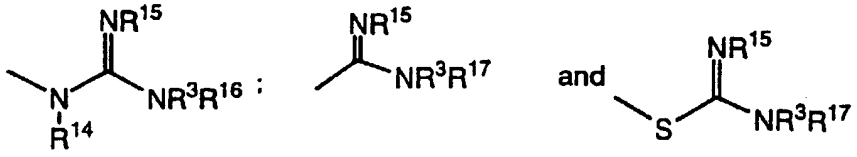
and

a C_{6-10} heterocyclic ring system substituted by R^8 and R^9 and containing 1-4 heteroatoms selected from N, S and O; where r is an integer from 0-1; R^6 and R^7 are independently selected from the group consisting of H, C_{1-6}alkyl, aryl, C_{1-6}alkylaryl, -$COOR^{10}$, -$CONR^{10}R^{11}$, -CN and -CF_3; R^8 and R^9 are independently selected from the group consisting of H, C_{1-6}alkyl, aryl, C_{1-6}alkylaryl, C_{1-4}alkyloxy, halogen, -NO_2, -$NR^{10}R^{11}$, -$NR^{10}COR^{11}$, -O-R^{10}, -O-COR^{10}, -$COOR^{10}$, -$CONR^{10}R^{11}$, -CN, -CF_3, -$SO_2NR^{10}R^{11}$ and C_{1-6}alkyl-O-R^{10}; and R^{10} and R^{11} are independently selected from the group consisting of

H, C_{1-6}alkyl, C_{1-3}alkylaryl and aryl;

and all optical isomers thereof.

27. The compound of Claim 26 where A is R^3; $-NR^3R^4$

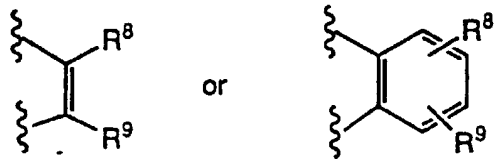


28. The compound of Claim 27 where R^3 and R^4 are independently selected from the group consisting of H, -OH and methyl.

29. The compound of Claim 26 where W is C_{1-4}alkyl, C_{5-6}cycloalkyl, aryl, or a five to ten membered heterocyclic ring system containing at least one N heteroatom.

30. The compound of Claim 26 where J is -S-, -O- or $-NR^5-$, where R^5 is H.

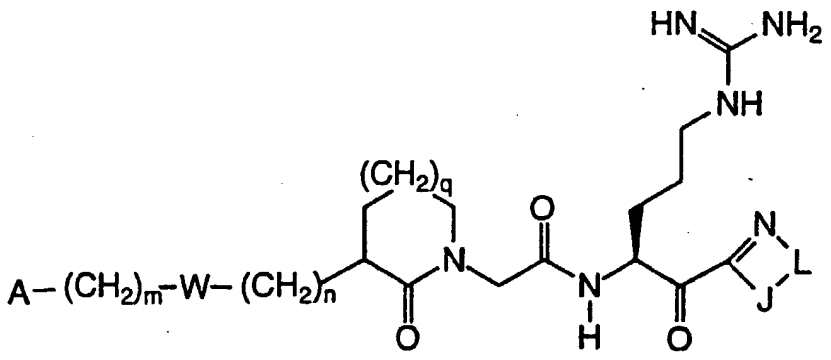
31. The compound of Claim 26 where L is:



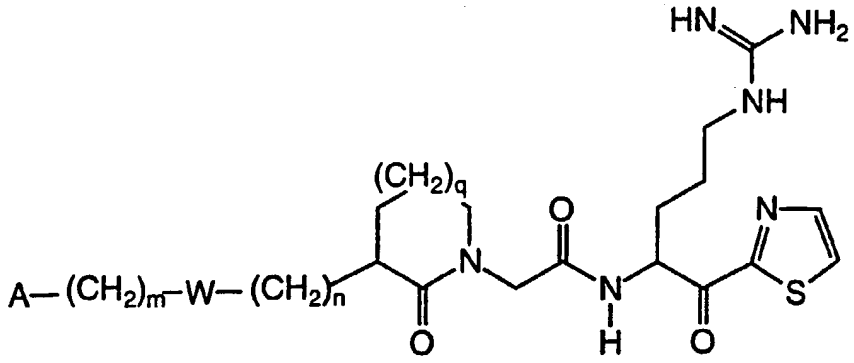
32. The compound of Claim 31 where R^8 is H, $-O-R^{10}$, $-COOR^{10}$, $-CONR^{10}R^{11}$ or $-CF_3$.

33. The compound of Claim 31 where R^9 is H, $-O-R^{10}$, $-COOR^{10}$, $-CONR^{10}R^{11}$ or $-CF_3$.

34. The compound of Claim 26 having the following stereochemistry:



35. A compound having the formula:



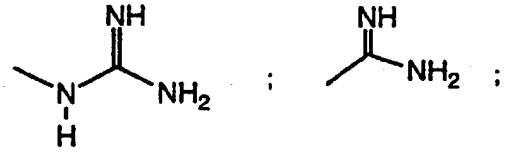
wherein:

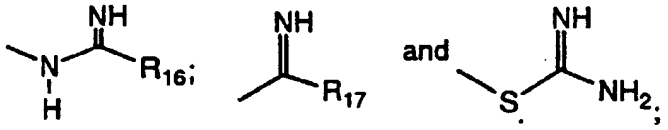
m is an integer from 0-3;

n is an integer from 0-6;

q is an integer from 0-2;

A is selected from the group consisting of R^3, $-NR^3R^4$,





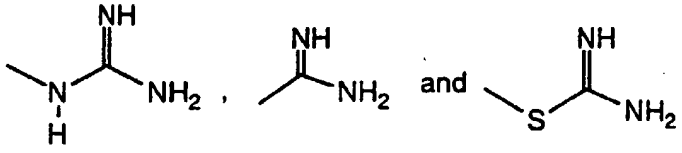
where R^3, R^4, R^{16} and R^{17} are independently selected from the group consisting of H, -OH

and C_{1-6}alkyl;

W is C_{1-6}alkyl, C_{3-8}cycloalkyl, C_{1-6}alkenyl, aryl, or a five to ten membered heterocyclic ring system containing 1-4 heteroatoms selected from the group consisting of N, O and S; with the proviso that when A is R^3, then W must contain at least one N atom;

and all optical isomers thereof.

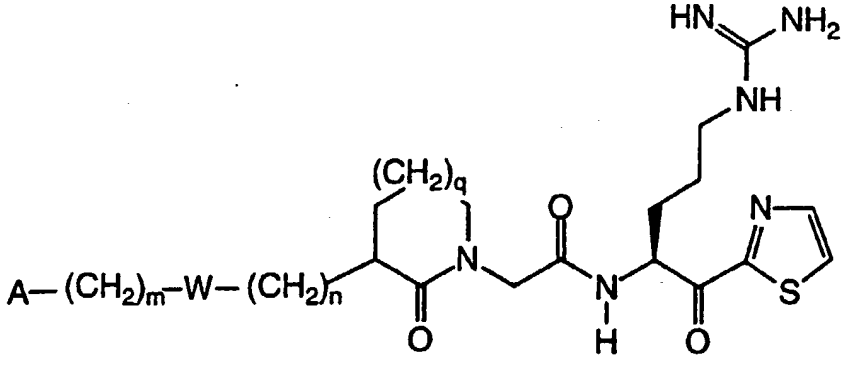
36. The compound of Claim 35 where A is selected from the group consisting of R^3,-NR^3R^4,



37. The compound of Claim 36 where R^3 and R^4 are independently selected from the group consisting of H, -OH and methyl.

38. The compound of Claim 35 where W is C_{1-4}alkyl, C_{5-6}cycloalkyl, aryl, or a five to ten membered heterocyclic ring system containing at least one N heteroatom.

39. The compound of Claim 35 having the following stereochemistry:



40. A pharmaceutical composition for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising a pharmaceutically acceptable carrier and the compound of claim 1.

41. A method for preventing or treating a condition in a mammal characterized by undesired thrombosis comprising administering to said mammal a therapeutically effective amount of the compound of claim 1.

42. The method of claim 41, wherein the condition is selected from the group consisting of: the treatment or prevention of unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, thrombotic stroke, embolic stroke, disseminated intravascular coagulation including the treatment of septic shock, deep venous thrombosis in the prevention of pulmonary embolism or the treatment of reocclusion or restenosis of reperfused coronary arteries, deep venous thrombosis, pulmonary embolism, myocardial infarction, stroke, thromboembolic complications of surgery and peripheral arterial occlusion, occlusive coronary thrombus formation resulting from either thrombolytic therapy or percutaneous transluminal coronary angioplasty, thrombus formation in the venous vasculature and disseminated intravascular coagulopathy.

43. A method for inhibiting the coagulation of biological samples, comprising the administration of the compound of claim 1.

INTERNATIONAL SEARCH REPORT

Inten. ..onal Application No
PCT/US 97/18647

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D417/14 C07F5/02 C07D417/12 A61K31/425

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 96 18644 A (CORVAS INTERNATIONAL, INC) 20 June 1996 cited in the application see claims	1-43
A	WO 95 35313 A (CORVAS INTERNATIONAL, INC) 28 December 1995 cited in the application see claims	1-43
A	WO 95 35311 A (CORVAS INTERNATIONAL, INC) 28 December 1995 see claims	1-43
A	US 5 523 308 A (COSTANZO MICHAEL J ET AL) 4 June 1996 see claims	1-43

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
26 January 1998	03-02-1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

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INTERNATIONAL SEARCH REPORT

Inter. ...nal Application No
PCT/US 97/18647

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 471 651 A (SANDOZ LTD) 19 February 1992 see claims ---	1-43
A	WO 96 19491 A (BIOCHEM PHARMA INC.) 27 June 1996 see claims -----	1-43

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/18647

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[] The additional search fees were accompanied by the applicant's protest.

[] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/US 97/18647

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

Claims Nos.: none

because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

The claims 1-25 are so broad that for determining the scope of a meaningful international search due account has been taken of rule 33.3 P.C.T.;special emphasis was put on the following subject-matter during the international search: examples,claims 26-39,compounds of pages 23-25

Remark : Although claims 41-43
are directed to a method of treatment of
the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter.. .onal Application No
PCT/US 97/18647

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inten. ..onal Application No
PCT/US 97/18647

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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Form PCT/ISA/210 (patent family annex) (July 1992)